DOI:
10.1093/ajcn/nqy376

Document Version
Peer reviewed version

Prebiotics in irritable bowel syndrome and other functional bowel disorders in adults: a systematic review and meta-analysis of randomized controlled trials

Authors

Bridgette Wilson, Megan Rossi, Eirini Dimidi, Kevin Whelan

Affiliation:

King's College London, Department of Nutritional Sciences, London, United Kingdom

Names for PubMed Indexing

Wilson, Rossi, Dimidi, Whelan

Corresponding author:

Professor Kevin Whelan, King's College London, Franklin Wilkins Building, 150 Stamford Street, London, United Kingdom, SE1 9NH, kevin.whelan@kcl.ac.uk, tel: +44 (0)20 7848 3858.

Sources of support:

This systematic review was part of a doctoral fellowship funded by Clasado Biosciences Ltd, a dietary supplement company that produce prebiotics. Clasado Biosciences Ltd played no role in the decision to undertake this systematic review, nor any role in its design, implementation, analysis or interpretation.

The authors have received research funding from government bodies including National Institute of Health Research (KW) and Medical Research Council (KW, MR), charities including Crohn's and Colitis UK (KW, BW), ForCrohns (MR, KW), Helmsley Charitable Trust (KW, MR) and Kenneth Rainin Foundation (KW) and industry bodies including Almond Board of California (KW, MR, ED), Clasado Biosciences (KW, BW), International Nut and Dried Fruit Council Foundation (KW, ED, MR), and Nestle (KW, ED).

Short running head

Prebiotics in functional bowel disorders

Abbreviations:

FBD	Functional bowel disorder

GOS	Galacto-oligosaccharide
IBS	Irritable bowel syndrome
ITF	Inulin type fructan
SMD	Standard mean difference
WMD	Weighted mean difference

ABSTRACT

Background

Irritable bowel syndrome (IBS) and other functional bowel disorders (FBD) are prevalent disorders with altered microbiota. Prebiotics positively augment gut microbiota and may offer therapeutic potential.

Objective

To investigate the effect of prebiotics compared to placebo on global response, gastrointestinal symptoms, quality of life (QoL) and gut microbiota, via systematic review and meta-analysis of randomized controlled trials (RCTs) in adults with IBS and other FBD.

Design

Studies were identified using electronic databases, back-searching reference lists and hand-searching abstracts. RCTs that compared prebiotics to placebo in adults with IBS or other FBD were included. Two reviewers independently performed screening, data extraction, and bias assessment. Outcome data were synthesized using odd ratios (OR), weighted mean differences (WMD) or standardized mean differences (SMD) using a random-effects model. Sub-analyses were performed for type of FBD and dose, type and duration of prebiotic.

Results

Searches identified 2332 records, and 11 RCTs were eligible (729 patients). Response to intervention was 52/97 (54%) for prebiotic and 59/94 (63%) for placebo, with no difference between groups (OR 0.62; 95%CI 0.07, 5.69; p=0.67). Similarly, no differences were found for severity of abdominal pain, bloating and flatulence, and quality of life score between prebiotics and placebo. However, flatulence severity was improved by prebiotics at doses ≤6 g/d (SMD -0.35, 95%CI -0.71, 0.00, p=0.05) and

by non-inulin type fructan prebiotics (SMD -0.34, 95%CI -0.66, -0.01, p=0.04), while inulin-type fructans worsened flatulence (SMD 0.85, 95%CI 0.23, 1.47, p=0.007). Prebiotics increased absolute abundance of bifidobacteria (WMD 1.16 log_{10} copies 16S rRNA gene; 95%CI 0.06, 2.26; p=0.04). No studies were at low risk of bias across all bias categories.

Conclusions

Prebiotics do not improve gastrointestinal symptoms or quality of life in patients with IBS or other FBD, but they do increase bifidobacteria. Variations in prebiotic type and dose impacted symptom improvement or exacerbation.

Keywords: Prebiotics, IBS, FBD, inulin type fructans, galactooligosaccharides

INTRODUCTION

Functional bowel disorders (FBD) are a ‘spectrum of chronic gastrointestinal disorders characterized by predominant symptoms or signs of abdominal pain, bloating, distension, and/or bowel habit abnormalities’ [1]. Irritable bowel syndrome (IBS) is characterized by abdominal pain associated with changes in defecation. Systematic reviews report a global prevalence of 11.2% for IBS [2], however recent surveys using updated definitions report a prevalence of 5.7% for IBS, 9.3% for functional diarrhea, 0.9% for functional bloating [3]. Not only are FBD and IBS prevalent disorders, they can impact quality of life, are a common cause of consultation with healthcare systems and treatment satisfaction is variable [4, 5].

IBS and other FBD share some aspects of etiology, some of which relate to the gut microbiota. Case-control studies report altered gut microbiota in the majority of people with IBS [6-8], a key feature of which is lower bifidobacteria [9], a microbial signature associated with a greater number of days of abdominal pain in both healthy adults and IBS [10, 11]. Further, gastrointestinal infection leads to a higher likelihood of developing both IBS or functional diarrhea, implicating the gut microbiota in these FBDs [12]. Low grade inflammation is present in some people with IBS, which may be mediated via gut microbiota signaling to the gastrointestinal immune system [13, 14]. Furthermore, altered pain signaling/visceral hypersensitivity has been reported in both IBS and functional bloating, which may be influenced by the effect of serotonin on enterochromaffin cells [1, 15].

Prebiotics are ‘substrates that are selectively utilized by host microorganisms conferring a health benefit to the host’ [16]. Prebiotics are typically dietary carbohydrates, with inulin-type fructans (ITF) (fructose polymers) and galactooligosaccharides (GOS) (galactose polymers) being the most extensively

studied, however, other novel classes of prebiotic are under investigation [17]. Extensive studies have demonstrated the capacity of prebiotics to specifically enhance the growth of bifidobacteria in healthy adults [18]. Additionally, prebiotics have been shown to increase fecal short chain fatty acids (SCFA) and reduce gut-associated inflammatory markers [14, 19], thus providing a mechanistic rationale for their role in managing symptoms in IBS and other FBD.

A systematic review published in 2014 [20] only identified one randomized controlled trial (RCT) of prebiotics in IBS [21] and its update identified only three RCTs [22] However, these systematic reviews were specific to IBS rather than more broadly to FBDs that may share a common etiology, presentation and overlapping symptoms [23] and the latest did not meta-analyze the three trials [22]. Therefore, the aim of this study was to investigate the effect of prebiotics compared to placebo on response, gastrointestinal symptoms, stool form and frequency, quality of life and gut microbiota, via a systematic review and meta-analysis of RCTs in adults with IBS or other FBD.

METHODS

This review was undertaken in line with recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [24] and reported in line with the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses [25]. Identification, screening, eligibility and inclusion of eligible papers were agreed between the researchers in advance and published prior to the literature search being conducted (PROSPERO CRD42017074072).

Eligibility criteria

The inclusion criteria were any RCTs reporting the effect of the administration of a prebiotic compared to a placebo on patients with IBS or other FBD. Details of the full inclusion and exclusion criteria are described in **Table 1**.

Studies of patients with functional constipation only were not included because the presenting symptoms and etiology do not completely overlap with other FBD (e.g. abdominal pain not a dominant feature as in IBS). In addition, as most prebiotics are fermentable, non-viscous and non-bulking, there is limited mechanistic rationale for prebiotics in functional constipation, and because higher bifidobacteria have been reported in functional constipation compared with other FBD, and therefore inclusion may have confounded the microbiota findings [26].

Search strategy

Studies were identified through systematic search of electronic databases, hand-searching of conference abstracts, clinical trial databases, and back-searching of reference lists of all eligible studies.

The following six electronic databases were searched: MEDLINE (US National Library of Medicine, USA; Ovid interface) from 1946 to November 2018; EMBASE (Elsevier B.V., The Netherlands; Ovid interface) from 1974 to November 2018; CINAHL (CINAHL Information Systems, USA, EBSCO host interface) from 1946 to 2018; CENTRAL (The Cochrane Library, Chichester, Wiley InterScience) for all years; and Web of Science (ISI Thomson Scientific, UK; Web of Knowledge portal) from 1900 to November 2018. The final search date was 8 November 2018. Combinations of the terms ‘prebiotics,’ ‘irritable bowel syndrome’ and ‘functional bowel disorder’ were searched for as MeSH headings and key or free text words. A list of the search strategy is presented in Supplemental Table 1.

Hand searching of abstracts from 2007 to 2018 from annual conferences of the following organizations was undertaken: Digestive Disease Week (*Gastroenterology*); British Society of Gastroenterology (*Gut*), United European Gastroenterology Week (*United European Gastroenterology J*); Gastroenterological Society of Australia (*J*

Gastroenterol Hepatol); European Society of Neurogastroenterology and Motility (*Neurogastroent Motil*); British Dietetic Association (*J Human Nutrition Dietetics*); Academy of Nutrition and Dietetics (*J Amer Dietetic Assoc* / *J Academy Nutrition Dietetics*); and the Dietitians Association of Australia (*Nutrition & Dietetics*).

The clinical trials databases of the World Health Organization (ISCTRN registry) and the US National Institute of Health (Clinicaltrials.gov) were also searched to identify completed but unpublished trials.

Screening

References were imported into a bibliographic database and duplicates were removed automatically (EndNote X7; Thomson Reuters). Titles and abstracts were screened against the eligibility criteria (Table 1) and two researchers then independently screened all potentially eligible full text articles against the eligibility criteria (BW, MR). The percentage agreement in study eligibility and a kappa statistic were calculated to check concordance between reviewers [24]. Disagreements about study eligibility were resolved through discussion with a third researcher (KW).

Data extraction

Data were extracted from each eligible study relating to the patient or group, the intervention, the comparator, outcomes measured and the study design, as detailed in Table 1. A standardized data extraction sheet was developed, and two reviewers extracted the data from eligible papers (BW, MR). Discrepancies were reviewed and resolved. Where papers contained insufficient or missing data, the corresponding author was contacted for further information.

The Cochrane risk of bias tool was used to assess each study individually. The two reviewers independently assessed risk of bias using seven domains: adequacy of randomization, allocation concealment, blinding methods, complete outcome data,

selective reporting and other sources of bias [24]. Percentage agreement and kappa statistic were calculated to check concordance between reviewers, and differences resolved by a third reviewer (KW) [24].

Data synthesis

Meta-analysis was performed where two or more studies reported data for the same outcome. Data for meta-analyses were entered into proprietary software (RevMan version 5.3; The Nordic Cochrane Centre, Cochrane Collaboration). For dichotomous outcomes (e.g. response), frequencies were entered to obtain an odds ratio (OR). For continuous outcomes that were reported in the same units and measured using the same tool, a weighted mean difference (WMD) was calculated, whereas for continuous outcomes that were measured or reported differently, a standardized mean difference (SMD) was calculated [27], using a random-effects model. For cross-over studies, the intervention and control periods were entered separately. Where a single study used several doses of a prebiotic, each dose was treated as a separate study for the meta-analysis, whereby the different prebiotic doses were compared to the control independently, with the sample size in the control group divided by the number of different doses to reduce effect-size error as recommended [24]. Forest plots with 95% CIs were generated for all outcomes.

Heterogeneity between results was assessed using the I^2 statistic and the chi-square test, a P-value <0.10 was used to define significant heterogeneity [24]. I^2 statistic values of 25%, 50% and 75% were defined as low, moderate and high heterogeneity, respectively [24]. Where heterogeneity was high and outlier studies were observed, sensitivity analysis was performed and data analysis with and without the outlier study was reported, as recommended [24]. Publication bias assessment was planned using funnel plot analysis if the number of available studies was >10.

Predefined subgroup analyses were planned to investigate differences by: (i) FBD subtypes (IBS, functional diarrhea etc.); (ii) prebiotic type (ITF, non-ITF); (iii) prebiotic dose; and (iv) prebiotic duration.

RESULTS

Study identification

A total of 2332 non-duplicated papers were identified by the search strategy. The titles and abstracts were reviewed and 35 were deemed potentially eligible (**Figure 1**). The two reviewers agreed on the eligibility (inclusion/exclusion) of 31/35 (89%) of the studies, with a kappa statistic of 0.74 representing substantial agreement [28]. Eleven studies fulfilled the inclusion criteria (**Table 2**).

Study Characteristics

The 11 eligible RCTs compared a prebiotic intervention to a placebo and involved 729 adult patients with either IBS (8 studies) or other FBD (3 studies). These consisted of seven studies of ITF, two studies of β-galactooligosaccharides, and one study each of partially-hydrolyzed guar gum and pectin powder. Ten studies were published in English and one in Chinese, which was then translated to English [29]. Ten studies were full articles and one was in abstract form only [30]. Corresponding authors of eight studies were contacted to obtain supplementary information. Of these, six replied [21, 30-34], and three provided data for inclusion in the analyses [30, 31, 34]. One study did not report the data on the outcomes of interest despite measuring these [33] and one study did not report any outcome data in a format that could be meta-analyzed [35]. Authors were contacted but no further data were supplied.

Clinical outcomes

The results of the meta-analyses are summarized in **Table 3**.

Response to treatment

Three studies measured dichotomous overall symptom response to treatment including 191 patients [32, 36, 37]. Overall, 52/97 (54%) patients responded to the prebiotic and 59/94 (63%) responded to placebo, with no significant difference between the groups (OR 0.62; 95% CI 0.07, 5.69; p=0.67; I^2=91%, p<0.00001)**.** Subgroup analysis was possible for FBD type, in which two studies of IBS alone showed no difference in the odds of response (OR 0.22; 95% CI 0.02, 2.74; p= 0.24; I^2=89% p=0.002) [32, 36], and for dose, in which two studies of prebiotics >6 g/d showed no difference in odds of response (OR 0.22; 95% CI 0.02, 2.74; p= 0.24; I^2=89% p=0.002) [32, 36], and duration, in which two studies ≥4-weeks showed no difference in odds of response (OR 1.88; 95% CI 0.27, 13.18; p=0.53; I^2=85%, p=0.01) [36, 37], compared with placebo.

Integrative symptom scores, abdominal pain, bloating and flatulence

A range of integrative symptom scores (subjective global assessment, IBS severity scoring system (IBS-SSS), visual analogue scales and Likert scales) were measured in eight studies and sufficient data were reported in seven studies including 538 patients [21, 29, 31, 32, 34, 36, 38]. Prebiotics did not result in a significant difference in integrative symptom scores compared to placebo (**Figure 2)**. Heterogeneity was high and an outlier was identified [34] and analysis with (SMD -0.39; 95% CI -1.43, 0.64; p=0.46; I^2=97%, p<0.00001) and without (SMD 0.12; 95% CI -0.22, 0.45; p=0.49; I^2=61%, p=0.02) the outlier was performed, which reduced but did not remove heterogeneity (Supplemental Figure 1). Two studies used the IBS-SSS to measure symptoms, including 185 patients [31, 38], however prebiotics did not result in a significantly different IBS-SSS score compared with placebo (WMD -5.4; 95% CI -35.7, 24.9; p=0.73; I^2=0%, p=0.59). The study that did not report data for overall symptoms did present graphs showing no difference in the overall symptoms scores between the

placebo group and prebiotic group after 4-weeks supplementation with 6 g/d of an ITF [33].

Severity of individual gastrointestinal symptoms were reported as follows: abdominal pain in ten studies with sufficient data reported in nine studies (628 patients) [21, 29-32, 34, 36-38], bloating in nine studies with sufficient data reported in eight studies (551 patients) [21, 29, 30, 32, 34, 36-38], and flatulence in seven studies with sufficient data reported in six studies (374 patients) [21, 32, 34, 36, 38]. Heterogeneity was high, and an outlier was identified for abdominal pain, bloating and flatulence [34], analysis with (Figure 2) and without this outlier was performed (Supplemental Figure 1). There were no significant differences in the severity of any of these symptoms between prebiotic and placebo, either with or without the outlier. The study that did not report data for symptom outcomes did present graphs that showed no difference in the severity of abdominal pain, bloating or flatulence between the placebo group and prebiotic group after 4-weeks supplementation with 8 g/d of an ITF [35].

Subgroup analyses of the effect on type of FBD, or of prebiotic type, dose and duration were performed. Due to the outlier contributing disproportionate heterogeneity to symptom outcomes, symptom analysis is presented here without the outlier and data including the outlier is presented as Online Supporting Material. There was no effect on integrative symptom scores, although severity of abdominal pain significantly improved in the study of FBD but not in the seven studies of IBS. Improvement in both abdominal pain and bloating severity with non-ITF prebiotics failed to reach statistical significance (**Figure 3**). Severity of flatulence significantly worsened with ITF prebiotics (Figure 3) (SMD 0.85; 95% CI 0.23, 1.47; p=0.007; I^2=57%, p=0.13) and significantly improved with both non-ITF (Figure 3) (SMD -0.34; 95% CI -0.66, -0.01; p=0.04; I^2=0%, p=0.78) and ≤6 g/d (**Figure 4**) (SMD -0.35; 95% CI -0.71, -0.00; p=0.050; I^2=0%,

p=0.51) . Data for subgroup analyses without the outlier are presented in Figures 3 and 4 and Supplemental figures 2 and 3. Data for subgroup analyses with the outlier included are presented in Supplemental figures 4-7.

Stool output

Stool frequency was measured in five studies [21, 30, 34, 36, 38] and stool consistency was measured in two studies [21, 34]. Data were not meta-analyzed as three of the five studies included all IBS-subtypes and one study did not categorize by predominant bowel habit making it not possible to define what a beneficial outcome would be as patients from either end of the stool output spectrum (IBS-diarrhea, IBS-constipation) were included. Of these studies, when comparing the effect of prebiotics, neither stool frequency nor consistency were different between prebiotic and placebo.

One study was conducted only in people with IBS-C however data were not compared between the placebo and prebiotic for stool frequency [30].

Two studies reported data for incomplete fecal evacuation (90 patients) [30, 37]. Prebiotics did not reduce severity of incomplete evacuation in patients with IBS or FBD (SMD 0.03; 95% CI -0.38, 0.45; p=0.88; I^2=0%, p=0.33).

Quality of life

Quality of life (QoL) was measured in four studies (322 patients) using either the validated IBS-QoL questionnaire or the IBS-36 questionnaire [21, 29, 34, 38]. Prebiotics did not affect QoL scores in IBS or FBD, and no outliers were identified (SMD 0.06; 95% CI -0.14, 0.25; p=0.57 I^2=0%, p=0.41). Neither doses of ≤6 g/d (SMD -0.02; 95% CI -0.21, 0.25; p=0.85 I^2=0%, p=0.56) or doses of >6 g/d (SMD 0.00; 95% CI -0.77, 0.76; p=0.1, I^2=59%, p=0.12) impacted QoL compared with placebo. Subgroup analysis on type of FBD and type or duration of prebiotic could not be performed due to insufficient studies in these subgroups.

Three studies used the validated IBS-QoL questionnaire (239 patients) [21, 29, 38]. There was no significant effect of prebiotics on IBS-QoL (SMD 0.00; 95% CI -0.31, 0.31; p=0.99 I^2=22%, p=0.28).

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) was measured in two studies (162 patients) [31, 34]. Prebiotics did not impact HADS scores in IBS or FBD (WMD -0.12; 95% CI -0.83, 0.58; p=0.73; I^2=0%, p=0.82). Anxiety was measured in three studies (171 patients) [21, 31, 37]. Prebiotics did not impact anxiety in IBS or FBD (SMD -0.23; 95% CI -0.54, 0.08; p=0.14; I^2=0%, p=0.76). Subgroup analyses were possible for two studies in IBS specifically showing that prebiotics did not impact anxiety (SMD -0.12; 95% CI -0.59, 0.25; p= 0.52; I^2=0%, p=1.00), two studies on prebiotic type showing that ITF did not impact anxiety (SMD -0.27; 95% CI -0.62, 0.09; p= 0.14; I^2=2%, p=0.31), and on two studies for dose showing that ≤6 g/d did not impact anxiety (SMD -0.24; 95% CI -0.57, 0.08; p= 0.14; I^2=0%, p=0.56). There were insufficient studies to meta-analyze the impact of prebiotic duration.

Depression was measured in two studies in IBS only (121 patients) using the HADS [21, 31]. Prebiotics did not impact depression (SMD -0.23; 95% CI -1.49, 1.02; p=0.71; I^2=0%, p=0.65).

Microbiota outcomes

Fecal microbiota was measured in four studies, [21, 29, 31, 35], with three studies reporting data for absolute abundance (measured using real-time polymerase chain reaction) [29, 31, 35] and one reporting only relative abundance (measured using fluorescence *in situ* hybridization) and authors were unable to provide further data [21]. Therefore, meta-analysis was conducted for absolute abundance only (**Figure 5**).

Bifidobacteria

Four studies measured bifidobacteria, three of which reported absolute abundance (200 patients) [29, 31, 35]. Prebiotics significantly increased bifidobacteria in IBS or FBDs (WMD 1.16 log_{10} copies of 16S rRNA gene; 95% CI 0.06, 2.26; p=0.04; I^2=92%, p<0.00001) (Figure 5). The study that did not provide absolute abundance reported significantly greater relative abundance of bifidobacteria for both 3.5 g/d and 7 g/d of β-galactooligosaccharide compared to placebo.

Subgroup analyses were possible for two studies of prebiotic type, showing that ITF increased bifidobacteria abundance (WMD 0.59 log_{10} copies of 16S rRNA gene; 95% CI 0.14, 1.03; p= 0.009; I^2=22% p=0.26), and two studies of prebiotic dose, showing that doses >6 g/d increased bifidobacteria abundance (WMD 1.55 log_{10} copies of 16S rRNA gene; 95% CI 0.31, 2.78; p= 0.01; I^2=88% p=0.004), compared with placebo. It was not possible for study duration to be meta-analyzed for subgroups as all relevant studies were 4-weeks or longer.

Lactobacilli

Two studies measured absolute abundance of lactobacilli (164 patients) [29, 31]. Prebiotics did not impact absolute abundance of lactobacilli in IBS or FBD (WMD 0.22 log_{10} copies of 16S rRNA gene; 95% CI -0.31, 0.75; p=0.41; I^2=66%, p=0.09). Two different prebiotics were used, ITF prebiotic (5 g/d) increased lactobacilli compared to the control [31] whereas 24 g/d of pectin did not [29] (Figure 5).

Safety outcomes

There were inadequate data to analyze the number of adverse events and some patients reported multiple adverse events. Four studies (355 patients) [21, 36-38] described the number of patients reporting adverse events, with no significant

difference between the prebiotic and placebo groups (OR 0.77; 95% CI 0.47, 1.26; p=0.30; I^2=0%; p=0.69).

Subgroup analyses were performed where possible and demonstrated no effect in studies of IBS only (OR 0.85; 95% CI 0.47, 1.55; p=0.59; I^2=0%; p=0.60) or for ITF (OR 0.71; 95% CI 0.39, 1.28; p=0.25; I^2=0%; p=0.68), non-ITF (OR 0.93; 95% CI 0.38, 2.28; p=0.87; I^2=0%; p=0.41), or for doses ≤6 g/d (OR 0.81; 95% CI 0.42, 1.55; p=0.53; I^2=0%; p=0.52), or doses of >6 g/d (OR 0.71; 95% CI 0.33, 1.54; p=0.39; I^2=0%; p=0.34). Subgroup analyses were not possible for prebiotic duration.

Risk of bias

The risk of bias for individual studies are presented in **Figure 6**. No studies were at low risk of bias for all categories and no categories were at low risk of bias across all studies

Data for abdominal pain was presented in 10 studies and therefore a funnel plot was constructed to detect publication bias (Supplemental figure 8). One study was visually identified to contribute to asymmetry [34] of the data. The asymmetry may be explained by true heterogeneity in effect size for this study or by sampling variation given it was the only study that recruited patients via a database [24].

DISCUSSION

This systematic review and meta-analysis identified 11 RCTs investigating the effect of prebiotics in IBS or other FBD on gastrointestinal symptoms, stool output, quality of life and gut microbiota. Based on the current body of evidence, overall, prebiotics do not benefit symptom management or improve quality of life in IBS or other FBD, however they do increase fecal bifidobacteria.

Meta-analysis showed prebiotics did not significantly impact integrative symptom scores, severity of abdominal pain, bloating or flatulence. However, there was

considerable heterogeneity in these symptom findings that was explained in part by the presence of an outlier study and to some degree by variations in prebiotic dose and type. For example, prebiotics at a dose of ≤6 g/d improved flatulence, but higher doses did not impact this or any other symptoms. Furthermore, ITF significantly worsened flatulence, whereas non-ITF (including GOS and guar gum) significantly improved flatulence. This highlights the importance of considering prebiotic dose and type in both clinical nutrition practice and research, as well as in the conduct of meta-analyses. Previous systematic reviews of prebiotics have synthesized data from RCTs in metabolic syndrome blood biomarkers [39] and chronic kidney disease [40] and reported significant heterogeneity when meta-analyzing outcomes. Few have performed subgroup analyses based upon prebiotic type and dose, which may be in part responsible for the heterogeneity, but also neutralizes any observed benefit or harm of specific prebiotic doses or types. For these reasons, meta-analyses of prebiotic interventions should perform subgroup analysis on prebiotic type and dose [41].

The analysis of the data without the outlier should be interpreted with caution and should be considered alongside the analyses of all studies together as presented in Figure 2 and Supplemental figures 4-7. The outlier study [34] reported significant benefit over placebo for all symptoms however the effect sizes were much greater than for similar studies including one that used a similar dose of the same prebiotic [21]. Therefore, symptom analysis was too heterogeneous to be able to detect meaningful differences when all data were combined. The reason for the results seen in this outlier is unclear except that the participants were selected from a database and this may have introduced recruitment bias.

Subgroup analysis of duration of prebiotics did not provide insight into the length of time a prebiotic should be trialed, although this is likely owing to the limited data

available. A recent proof of concept study in healthy adults supplemented with 2.8 g/d of GOS for three weeks reported an adaptation period where initial consumption led to increased flatulence, which had subsided by three weeks, indicating that patients should take a prebiotic for a minimum of three weeks to ascertain if it will be of benefit to them [42].

The gut-brain axis is a mechanism hypothesized to be involved in the etiology of IBS and other FBD. Patients with IBS score lower on QOL scales than healthy controls and IBS is associated with anxiety related co-morbidities [4, 5]. The meta-analysis did not support a role for prebiotics in improving QOL, anxiety or depression in patients with IBS or other FBD, neither did subgroup analysis find any effect for dose, type or duration of prebiotics. However, only four studies included quality of life and/or psychological outcome measures and each of the four used a different type of prebiotic making the results too heterogenous to draw firm conclusions.

The majority of the RCTs that have investigated the effect of prebiotics on IBS and other FBD used ITF, with subgroup analysis showing a worsening of flatulence. This is in line with current understanding of one of the mechanisms underpinning a diet commonly used for treating IBS that is low in ITF and other fermentable oligo-, di-, mono- saccharides and polyols (low FODMAP diet). The low FODMAP diet aims to reduce small bowel water content and colonic gas production through specific carbohydrate restriction [43]. Clinical trials have shown that the low FODMAP diet is effective in managing symptoms in 50-80% of patients with IBS, although the effect on the gastrointestinal microbiota may be of concern as it has been shown to specifically reduce fecal bifidobacteria [44, 45]. Further, the low FODMAP diet has been demonstrated to alleviate common symptoms of FBDs and IBS such as loose stool, urgency, abdominal bloating, abdominal pain and flatulence [44-47].

Due to the effectiveness of restricting fermentable carbohydrates on the low FODMAP diet, it seems contradictory that supplementation with prebiotic fermentable carbohydrates would also decrease symptoms in IBS and may relate to differences in chemical structure and microbial metabolism. The GOS in foods such as beans, pulses and legumes are α-GOS (i.e. raffinose, stachyose and verbascose) and produce gas on fermentation and are therefore restricted on the low FODMAP diet along with ITF [48]. However, non-ITF prebiotic supplements that were shown to significantly reduce flatulence (with the effect on abdominal pain and bloating approaching significance) in the current meta-analysis included β-GOS, which in contrast to α-GOS, are specifically metabolized by bifidobacteria that produce less gas [17, 49]. Further, frequency of mild distension, borborygmi and flatulence increased with ITF dose in healthy adults, and short-chain ITF are fermented more rapidly than longer chain ITF indicating that both the dose and structure of prebiotics are important [50]. ITF stimulate similar volumes of colonic gas in both healthy individuals and patients with IBS, however the induction of abdominal pain and discomfort only occurs in the latter [51]. This suggests that IBS is more complex than merely the volume of colonic gas production and is likely related to colonic hypersensitivity.

Although not included in this review, the use of prebiotics in functional constipation has been investigated in two systematic reviews [20, 52], identifying three trials [53-55]. In elderly subjects, prebiotics increased bifidobacteria and led to increased passage of stool and softer stool form compared to placebo [53, 54], however in women with constipation a mixture of ITF and PHGG (doses undefined) showed no benefit over placebo for any symptoms [55].

Gastrointestinal microbiota is implicated in IBS, with acute gastroenteritis and water-borne infections increasing the odds of developing IBS up to eight years later [56, 57].

In the current study it was found that prebiotic supplementation significantly increased fecal bifidobacteria abundance compared to placebo in patients with IBS and other FBD. A recent meta-analysis confirmed that established prebiotic fibers (ITF, GOS) and novel prebiotic fibers (e.g. arabinoxylan-oligosaccharide, manno-oligosaccharide, resistant starch, xylo-oligosaccharide) increase bifidobacteria in healthy people, whereas non-prebiotic fibers did not [18]. This meta-analysis confirms these findings in people with IBS with both β-GOS and pectin powder, demonstrating an increase in relative and absolute abundance of bifidobacteria respectively [21, 29]. One mechanism of action of prebiotics in IBS may therefore be the modulation of the altered microbiota. Although proving the prebiotic effect is a mechanism, and not merely an epiphenomenon, in any potential clinical effect in IBS is challenging given the lack of validated animal models of IBS that would enable microbiome manipulation.

This is the largest systematic review and only meta-analysis to investigate the effect of prebiotic supplementation in IBS and other FBD on response, gastrointestinal symptoms, quality of life and gut microbiota. Broad inclusion criteria were used to identify all placebo-controlled trials to shed light on this under-researched, yet clinically-relevant question. As a consequence, the broad inclusion criteria enabled the inclusion of one study that was designed to investigate if high-dose ITF prebiotics (19 g/d) could induce symptoms compared to a placebo in patients that had previously responded to a low FODMAP diet [32]. It is likely that this introduced significant bias in favor of the placebo. Nonetheless, when this study was excluded from the meta-analysis the overall findings for response (OR 1.88, 95% CI 0.27, 13.18, P=0.53) and integrative symptom score (SMD -0.02, 95% CI -0.22, 0.17, P=0.83) remained non-significant.

This meta-analysis used a robust design in line with PRISMA guidelines and the protocol was defined and published prior to the literature searches taking place, thus

limiting the potential for reviewer bias. However, the findings are limited by the small number of RCTs conducted. A further limitation is the varied methodology used by authors in defining IBS and other FBD. The data were largely heterogeneous but overall suggested that the net effect of prebiotics on clinical outcomes is neutral. Non-ITF prebiotics show some promise in individual symptom improvement however these results came from pooling data from different types of prebiotics and so the strength of this conclusion is weak.

Conclusion

In conclusion the current review suggests that overall prebiotics do not affect response, gastrointestinal symptoms or quality of life in patients with FBD or IBS, but they do increase bifidobacteria. Further, subgroup analysis revealed that neither type, dose nor duration influenced overall symptoms. Differences were seen between type and dose on individual symptoms, including that non-ITF prebiotics improved flatulence whereas ITF worsened flatulence, whilst prebiotics at a dose of ≤6 g/d reduced flatulence whereas higher doses had no effect. This review did not find sufficient evidence to establish an optimal duration of treatment.

Overall the quality of evidence is poor across studies investigating the effect of prebiotics on symptoms, QoL and microbiota in IBS and FBD, and this review highlights the need for more clinical trials of robust design and may direct future researchers towards lower dose, novel prebiotics rather than conducting further trials of ITF type prebiotics in patients with IBS or FBD. Further studies investigating the role of non-ITF and of novel prebiotics in symptom management and modulation of gut microbiota in IBS and other FBD should be performed in order to clarify the compounds most likely to impact symptoms.

Acknowledgements

BW, MR and KW designed the systematic review protocol, BW conducted the search, BW and MR independently reviewed studies against inclusion and exclusion criteria, extracted data and performed risk of bias assessment. BW and ED conducted meta-analysis. BW, ED and KW wrote the manuscript. All authors reviewed, edited and approved the final manuscript.

This systematic review was part of a doctoral fellowship funded by Clasado Biosciences Ltd, a dietary supplement company that produce prebiotics. Clasado Biosciences Ltd played no role in the decision to undertake this systematic review, nor any role in its design, implementation, analysis or interpretation.

The authors have received research funding from government bodies including National Institute of Health Research (KW) and Medical Research Council (KW, MR), charities including Crohn's and Colitis UK (KW, BW), ForCrohns (MR, KW), Helmsley Charitable Foundation (KW, MR) and Kenneth Rainin Foundation (KW) and industry bodies including Almond Board of California (KW, MR, ED), Clasado Biosciences (KW, BW), International Nut and Dried Fruit Council Foundation (KW, ED, MR), and Nestle (KW, ED).

References

1. Lacy, B.E., Mearin, F., Chang, L., Chey, W.D., Lembo, A.J., Simren, M., and Spiller, R., Bowel disorders. *Gastroenterology*, 2016. **150**(6): p. 1393-1407e1395.
2. Lovell, R.M. and Ford, A.C., Global prevalence of and risk factors for irritable bowel syndrome: A meta-analysis. *Clin. Gastroenterol. Hepatol.*, 2012. **10**(7): p. 712-721. e714.
3. Palsson, O.S., Whitehead, W.E., Van Tilburg, M.A., Chang, L., Chey, W., Crowell, M.D., Keefer, L., Lembo, A.J., Parkman, H.P., and Rao, S.S., Development and validation of the rome iv diagnostic questionnaire for adults. *Gastroenterology*, 2016. **150**(6): p. 1481-1491.
4. Nellesen, D., Yee, K., Chawla, A., Lewis, B.E., and Carson, R.T., A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. *J. Manag. Care Pharm.*, 2013. **19**(9): p. 755-764.
5. Gralnek, I.M., Hays, R.D., Kilbourne, A., Naliboff, B., and Mayer, E.A., The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology*, 2000. **119**(3): p. 654-660.
6. Rajilic-Stojanovic, M., Biagi, E., Heilig, H.G., Kajander, K., Kekkonen, R.A., Tims, S., and de Vos, W.M., Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology*, 2011. **141**(5): p. 1792-1801.
7. Jeffery, I.B., O'Toole, P.W., Ohman, L., Claesson, M.J., Deane, J., Quigley, E.M., and Simren, M., An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. *Gut*, 2012. **61**(7): p. 997-1006.
8. Casen, C., Vebø, H., Sekelja, M., Hegge, F., Karlsson, M., Ciemniejewska, E., Dzankovic, S., Frøyland, C., Nestestog, R., and Engstrand, L., Deviations in human gut microbiota: A novel diagnostic test for determining dysbiosis in patients with ibs or ibd. *Alimentary pharmacology & therapeutics*, 2015. **42**(1): p. 71-83.
9. Liu, H.-N., Wu, H., Chen, Y.-Z., Chen, Y.-J., Shen, X.-Z., and Liu, T.-T., Altered molecular signature of intestinal microbiota in irritable bowel syndrome patients compared with healthy controls: A systematic review and meta-analysis. *Dig. Liver Dis.*, 2017. **49**(4): p. 331-337.
10. Parkes, G.C., Rayment, N.B., Hudspith, B.N., Petrovska, L., Lomer, M.C., Brostoff, J., Whelan, K., and Sanderson, J.D., Distinct microbial populations exist in the mucosa-associated microbiota of sub-groups of irritable bowel syndrome. *Neurogastroenterol. Motil.*, 2012. **24**(1): p. 31-39.
11. Jalanka-Tuovinen, J., Salonen, A., Nikkila, J., Immonen, O., Kekkonen, R., Lahti, L., Palva, A., and de Vos, W.M., Intestinal microbiota in healthy adults: Temporal analysis reveals individual and common core and relation to intestinal symptoms. *PLoS One*, 2011. **6**(7): p. e23035.
12. Zanini, B., Ricci, C., Bandera, F., Caselani, F., Magni, A., Laronga, A.M., and Lanzini, A., Incidence of post-infectious irritable bowel syndrome and functional intestinal disorders following a water-borne viral gastroenteritis outbreak. *The American journal of gastroenterology*, 2012. **107**(6): p. 891.
13. Vicario, M., González-Castro, A.M., Martínez, C., Lobo, B., Pigrau, M., Guilarte, M., de Torres, I., Mosquera, J.L., Fortea, M., and Sevillano-Aguilera, C., Increased humoral

immunity in the jejunum of diarrhoea-predominant irritable bowel syndrome associated with clinical manifestations. *Gut*, 2014: **64**:1379-1388.

14. Vulevic, J., Juric, A., Walton, G.E., Claus, S.P., Tzortzis, G., Toward, R.E., and Gibson, G.R., Influence of galacto-oligosaccharide mixture (b-gos) on gut microbiota, immune parameters and metabonomics in elderly persons. *Br. J. Nutr.*, 2015: **114**: 586-595.
15. Barbara, G., Cremon, C., De Giorgio, R., Dothel, G., Zecchi, L., Bellacosa, L., Carini, G., Stanghellini, V., and Corinaldesi, R., Mechanisms underlying visceral hypersensitivity in irritable bowel syndrome. *Current gastroenterology reports*, 2011. **13**(4): p. 308-315.
16. Gibson, G.R., Hutkins, R., Sanders, M.E., Prescott, S.L., Reimer, R.A., Salminen, S.J., Scott, K., Stanton, C., Swanson, K.S., and Cani, P.D., Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology*, 2017; **14**:491-502.
17. Wilson, B. and Whelan, K., Prebiotic inulin-type fructans and galacto-oligosaccharides: Definition, specificity, function, and application in gastrointestinal disorders. *J. Gastroenterol. Hepatol.*, 2017. **32**: p. 64-68.
18. So, D., Whelan, K., Rossi, M., Morrison, M., Holtmann, G., Kelly, J.T., Shanahan, E.R., Staudacher, H.M., and Campbell, K.L., Dietary fiber intervention on gut microbiota composition in healthy adults: A systematic review and meta-analysis. *The American journal of clinical nutrition*, 2018. **107**(6): p. 965-983.
19. O'Keefe, S.J., Li, J.V., and Lahti, L., Fat, fibre and cancer risk in african americans and rural africans. 2015. **6**: p. 6342.
20. Ford, A.C., Quigley, E.M., Lacy, B.E., Lembo, A.J., Saito, Y.A., Schiller, L.R., Soffer, E.E., Spiegel, B.M., and Moayyedi, P., Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: Systematic review and meta-analysis. *The American journal of gastroenterology*, 2014. **109**(10): p. 1547-1562.
21. Silk, D., Davis, A., Vulevic, J., Tzortzis, G., and Gibson, G. *Clinical trial: The effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome*. Alimentary pharmacology & therapeutics, 2009. **29**, 508-518 DOI: 10.1111/j.1365-2036.2008.03911.x.
22. Ford, A.C., Harris, L.A., Lacy, B.E., Quigley, E.M., and Moayyedi, P., Systematic review with meta-analysis: The efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Alimentary pharmacology & therapeutics*, 2018. **48**(10): p. 1044-1060.
23. Simrén, M., Barbara, G., Flint, H.J., Spiegel, B.M., Spiller, R.C., Vanner, S., Verdu, E.F., Whorwell, P.J., and Zoetendal, E.G., Intestinal microbiota in functional bowel disorders: A rome foundation report. *Gut*, 2012; **62**:159-176.
24. Higgins, J.P. and Green, S., *Cochrane handbook for systematic reviews of interventions*. 5.1.0; 2011, The Cochrane Collaboration, Available from www.handbook.cochrane.org.
25. Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P., Kleijnen, J., and Moher, D., The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *Ann. Intern. Med.*, 2009. **151**(4): p. W-65-W-94.
26. Parkes, G.C., Brostoff, J., Whelan, K., and Sanderson, J.D., Gastrointestinal microbiota in irritable bowel syndrome: Their role in its pathogenesis and treatment. *Am. J. Gastroenterol.*, 2008. **103**(6): p. 1557-1567.

27. Cohen, J., Statistical power analysis for the behavioural sciences 2 edition lawrence erlbaum associates*. Hillsdale, NJ*, 1988.
28. Landis, J.R. and Koch, G.G., The measurement of observer agreement for categorical data*. Biometrics*, 1977. **33**(1): p. 159-174.
29. Xu, L., Yu, W., Jiang, J., Feng, X., and Li, N., [efficacy of pectin in the treatment of diarrhea predominant irritable bowel syndrome]*. Zhonghua Wei Chang Wai Ke Za Zhi*, 2015. **18**(3): p. 267-271.
30. Isakov, V., Pilipenko, V., Shakhovskaya, A., and Tutelyan, V., Efficacy of inulin enriched yogurt on bowel habits in patients with irritable bowel syndrome with constipation: A pilot study*. FASEB J.*, 2013. **27 (abstr)**.
31. Azpiroz, F., Dubray, C., Bernalier-Donadille, A., Cardot, J.M., Accarino, A., Serra, J., Wagner, A., Respondek, F., and Dapoigny, M., Effects of scfos on the composition of fecal microbiota and anxiety in patients with irritable bowel syndrome: A randomized, double blind, placebo controlled study*. Neurogastroenterol. Motil.*, 2017. **29 (2) (no pagination)**(e12911).
32. Shepherd, S., Parker, F., Muir, J., and Gibson, P. *Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: Randomized placebo-controlled evidence*. Clin. Gastroenterol. Hepatol., 2008. **6**, 765-771 DOI: 10.1016/j.cgh.2008.02.058.
33. Hunter, J., Tuffnell, Q., and Lee, A., Controlled trial of oligofructose in the management of irritable bowel syndrome*. J Nutr*, 1999. **129**(7): p. 1451S-1453s.
34. Vulevic, J., Tzortzis, G., Juric, A., and Gibson, G.R., Effect of a prebiotic galactooligosaccharide mixture (b-gos®) on gastrointestinal symptoms in adults selected from a general population who suffer with bloating, abdominal pain, or flatulence*. Neurogastroenterol. Motil.*, 2018: p. e13440.
35. Azpiroz, F., Molne, L., Mendez, S., Nieto, A., Manichanh, C., Mego, M., Accarino, A., Santos, J., Sailer, M., Theis, S., et al., Effect of chicory-derived inulin on abdominal sensations and bowel motor function*. J. Clin. Gastroenterol.*, 2017. **51**(7): p. 619-625.
36. Olesen, M. and Gudmand-Hoyer, E., Efficacy, safety, and tolerability of fructooligosaccharides in the treatment of irritable bowel syndrome*. Am J Clin Nutr*, 2000. **72**(6): p. 1570-1575.
37. Paineau, D., Payen, F., Panserieu, S., Coulombier, G., Sobaszek, A., Lartigau, I., Brabet, M., Galmiche, J., Tripodi, D., Sacher-Huvelin, S., et al. *The effects of regular consumption of short-chain fructo-oligosaccharides on digestive comfort of subjects with minor functional bowel disorders*. Br. J. Nutr., 2008. **99**, 311-318 DOI: 10.1017/S000711450779894X.
38. Niv, E., Halak, A., Tiommny, E., Yanai, H., Strul, H., Naftali, T., and Vaisman, N. *Randomized clinical study: Partially hydrolyzed guar gum (phgg) versus placebo in the treatment of patients with irritable bowel syndrome*. Nutr. Metab. (Lond.), 2016. **13**:10 DOI: 10.1186/s12986-016-0070-5.
39. Beserra, B.T., Fernandes, R., do Rosario, V.A., Mocellin, M.C., Kuntz, M.G., and Trindade, E.B., A systematic review and meta-analysis of the prebiotics and synbiotics effects on glycaemia, insulin concentrations and lipid parameters in adult patients with overweight or obesity*. Clin. Nutr.*, 2015. **34**(5): p. 845-858.
40. Rossi, M., Klein, K., Johnson, D.W., and Campbell, K.L., Pre-, pro-, and synbiotics: Do they have a role in reducing uremic toxins? A systematic review and meta-analysis*. Int j of nephrol*, 2012; **2012** 10.1155/2012/673631.
41. Whelan, K., Editorial: The importance of systematic reviews and meta-analyses of probiotics and prebiotics*. Am. J. Gastroenterol.* 2014 **109**:1563-5.

42. Mego, M., Accarino, A., Tzortzis, G., Vulevic, J., Gibson, G., Guarner, F., and Azpiroz, F., Colonic gas homeostasis: Mechanisms of adaptation following host-g904 galactooligosaccharide use in humans. *Neurogastroenterol. Motil.*, 2017. **29**: e13080.
43. Murray, K., Wilkinson-Smith, V., Hoad, C., Costigan, C., Cox, E., Lam, C., Marciani, L., Gowland, P., and Spiller, R.C., Differential effects of fodmaps (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by mri. *Am. J. Gastroenterol.*, 2014. **109**(1): p. 110-119.
44. Staudacher, H., Lomer, M., Farquharson, F., Louis, P., Fava, F., Franciosi, E., Scholz, M., Tuohy, K., Lindsay, J., Irving, P., Whelan, K., Diet low in fodmaps reduces symptoms in patients with irritable bowel syndrome and probiotic restores bifidobacterium species: A randomized controlled trial. *Gastroenterology*, 2017, **153**, 936-947.
45. Schumann, D., Klose, P., Lauche, R., Dobos, G., Langhorst, J., and Cramer, H., Low fermentable, oligo-, di-, mono-saccharides and polyol diet in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. *Nutrition*, 2018. **45**: p. 24-31.
46. Staudacher, H., Lomer, M., Anderson, J., Barrett, J., Muir, J., Irving, P., and Whelan, K. *Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome*. J Nutr, 2012. **142**, 1510-1518 DOI: 10.3945/jn.112.159285.
47. McIntosh, K., Reed, D.E., Schneider, T., Dang, F., Keshteli, A.H., De Palma, G., Madsen, K., Bercik, P., and Vanner, S., Fodmaps alter symptoms and the metabolome of patients with ibs: A randomised controlled trial. *Gut*, 2016: **66**:1241-1251.
48. Whelan, K., Martin, L.D., Staudacher, H.M., and Lomer, M.C.E., The low fodmap diet in the management of irritable bowel syndrome: An evidence-based review of fodmap restriction, reintroduction and personalisation in clinical practice. *J. Hum. Nutr. Diet.*, 2018. **31**(2): p. 239-255.
49. Vulevic, J., Rastall, R.A., and Gibson, G.R., Developing a quantitative approach for determining the in vitro prebiotic potential of dietary oligosaccharides. *FEMS Microbiol. Lett.*, 2004. **236**(1): p. 153-159.
50. Rumessen, J.J. and Gudmand-Høyer, E., Fructans of chicory: Intestinal transport and fermentation of different chain lengths and relation to fructose and sorbitol malabsorption. *The American journal of clinical nutrition*, 1998. **68**(2): p. 357-364.
51. Major, G., Pritchard, S., Murray, K., Alappadan, J., Hoad, C., Marciani, L., Gowland, P., and Spiller, R. *Colon hypersensitivity to distension, rather than excessive gas production, produces carbohydrate-related symptoms in individuals with irritable bowel syndrome*. Gastroenterology, 2017. **152**, 124-133.e122 DOI: 10.1053/j.gastro.2016.09.062.
52. Christodoulides, S., Dimidi, E., Fragkos, K.C., Farmer, A.D., Whelan, K., and Scott, S.M., Systematic review with meta-analysis: Effect of fibre supplementation on chronic idiopathic constipation in adults. *Alimentary Pharmacology & Therapeutics*, 2016. **44**(2): p. 103-116.
53. Surakka, A., Kajander, K., Rajilic, M., Karjalainen, H., Hatakka, K., Vapaatalo, H., Zoetendal, E., De Vos, W., Korpela, R., and Tynkkynen, S., Yoghurt containing galactooligosaccharides facilitates defecation among elderly subjects and selectively increases the number of bifidobacteria. *International Journal of Probiotics and Prebiotics*, 2009. **4**(1): p. 65-74.
54. Marteau, P., Jacobs, H., Cazaubiel, M., Signoret, C., Prevel, J.-M., and Housez, B., Effects of chicory inulin in constipated elderly people: A double-blind controlled trial. *Int. J. Food Sci. Nutr.*, 2011. **62**(2): p. 164-170.

55. Linetzky Waitzberg, D., Pereira, C., Logullo, L., Manzoni Jacintho, T., Almeida, D., Teixeira da Silva, M., and Torrinhas, M., Microbiota benefits after inulin and partially hydrolized guar gum supplementation-a randomized clinical trial in constipated women. *Nutr. Hosp.*, 2012: **27**; 123-129.
56. Marshall, J.K., Thabane, M., Garg, A.X., Clark, W.F., Moayyedi, P., Collins, S.M., and Walkerton Health Study, I., Eight year prognosis of postinfectious irritable bowel syndrome following waterborne bacterial dysentery. *Gut*, 2010. **59**(5): p. 605-611.
57. Porter, C.K., Gormley, R., Tribble, D.R., Cash, B.D., and Riddle, M.S., The incidence and gastrointestinal infectious risk of functional gastrointestinal disorders in a healthy us adult population. *Am. J. Gastroenterol.*, 2011. **106**(1): p. 130-138.

Table 1: Table of inclusion and exclusion criteria following the PICOS[1] approach

PICOS[1]	Inclusion and exclusion criteria	Data extraction
Participants	Adult populations ≥18 and ≤64 with IBS (any subtype) or FBD as defined by the authors were included. Studies with a median age between these values were eligible. Participants with drug-induced constipation or diarrhea, inflammatory bowel disease, acute gastrointestinal disorders (e.g. traveler's diarrhea) or functional constipation alone were excluded, unless data specifically for participants with IBS or other FBD alone could be extracted.	Age, sex, IBS subtype, type of FBD, method for diagnosis, setting, location, number of patients of each IBS-subtype randomized to intervention and comparator groups, inclusion and exclusion criteria.
Intervention	Prebiotics defined as ITF, GOS, or any other compound defined by the author as a prebiotic if justification for the compound fulfilling criteria as a prebiotic were explicitly stated. Prebiotics to be administered at a dose of >1 g/d for a minimum of one week and could be presented as powders, capsules, tablets, softgel, or fortified food forms. Trials that included other interventions (e.g. drug use) were included if the effect of the prebiotic alone could be isolated. Multiple intervention arms were eligible. Trials of symbiotic were excluded, unless there was an arm of prebiotic alone.	Prebiotic type, dose, frequency, formulation, extraction method, degree of polymerization, degree of purity and duration of intervention, compliance.
Comparators	Only trials that used a placebo control were eligible. The effect of the prebiotic alone had to be able to be isolated. Trials where the comparator did not allow the effect of the prebiotic alone to be isolated were excluded (e.g. prebiotic *versus* probiotic).	Type and dose of comparator, compliance.

Outcomes	Trials reporting clinical subjective and objective outcome data including IBS or other FBD response, symptoms, quality of life, stool form and frequency and gut microbiota were included.	Outcomes measured, method of assessment. Acceptability and compliance measures, and adverse events.
Study design	Only randomized controlled trials with ≥2 study groups, where it was possible to extract data on just the prebiotic *vs* placebo interventions were included. Both parallel and crossover trial design were eligible.	Type of study design, intention to treat analysis, number of excluded patients, adequacy of randomization and blinding methods of participants and investigators.

[1]PICOS: Participants, Intervention, Comparator, Outcome, Study type; IBS: Irritable Bowel Syndrome; FBD: Functional Bowel Disorder.

Table 2: Characteristics of eligible studies

Study	Country	Trial Design	Blinding	Outcomes Included in Meta-analysis	Sample size (% female)	FBD or IBS (subtypes)	Prebiotic	Form	Dose	Duration
Azpiroz 2017a [35]	Spain	Parallel	Double	Symptoms, microbiota	40 (NR)	FBD unclassified	Inulin	Powder	8 g/d	4 weeks
Azpiroz 2017b [31]	France and Spain	Parallel	Double	Symptoms, microbiota	79 (39)	IBS (all subtypes)	Short-chain fructo-oligosaccharide	Powder	5 g/d	4 weeks
Hunter 2009 [33]	UK	Cross-over	Double	Symptoms	21 (81)	IBS (all subtypes)	Oligofructose	Powder	6 g/d	4 weeks
Isakov 2013 [30]	Russia	Parallel	Unclear	Symptoms	40 (NR)	IBS-C	Inulin	Yogurt	3 g/d	2 weeks
Niv 2016 [38]	Israel	Parallel	Double	Symptoms, QoL	108 (66)	IBS (all subtypes)	Partially hydrolyzed guar gum	Powder sachet	6 g/d (3 g/d for first week)	12 weeks
Olesen and Gudmand-Hoyer 2000 [36]	Denmark	Parallel	Double	Symptoms	98 (82)	IBS (all subtypes)	Fructo-oligosaccharide	Powder	20 g/d (10 g/d for first two weeks)	12 weeks
Paineau 2008 [37]	France	Parallel	Double	Symptoms, QoL	105 (NR)	FBD mixed	Short-chain fructo-oligosaccharide	Powder	5 g/d	6 weeks
Shepherd 2008 [32]	Australia	Cross-over	Double	Symptoms	24 (92)	IBS (all subtypes) LFD responsive + fructose malabsorption	Oligofructose	Orange flavored drink	19 g/d (7 g for 3-days, 14 g for 3-days 19 g for 8-days)	2 weeks

Silk 2009 [21]	UK	Parallel	Double	Symptoms, QoL, microbiota	44 (64)	IBS (all subtypes)	β-galactooligosaccharide	Flavored powder	3.5 g/d or 7 g/d	4 weeks
Vulevic 2018 [34]	UK	Cross-over	Double	Symptoms, QoL	83 (57)	FBD (moderate to severe)	β-galactooligosaccharide	Powder	2.75 g/d	2 weeks
Xu 2015 [29]	China	Parallel	Double	Symptoms, QoL, microbiota	87 (55)	IBS-D	Pectin powder	Powder	24 g/d	6 weeks

All trials except Vulevic (2018) [34] were conducted in primary care setting and all included a placebo control group or treatment period if cross-over design was used.

NR: not reported; LFD: low FODMAP diet; QoL: Quality of life, IBS: irritable bowel syndrome, FBD: functional bowel disorder

Table 3: Results of the meta-analysis comparing prebiotics to placebo for symptoms, quality of life, microbiota and adverse events in patients with IBS or FBD

			Results		Heterogeneity		
Outcome	No of studies in meta-analysis (reference nos.)	Patients (n)	Meta-analysis overall estimate (95% CI)	P	Chi-square test	P	I^2 (%)
Response to treatment	3 [32, 36, 37]	191	OR 0.62 (0.07, 5.69)	0.67	21.47	<0.00001	91
IBS-SSS	2 [31, 38]	185	WMD -5.40 (-35.70, 24.90)	0.73	0.3	0.59	0
Incomplete evacuation	2 [30, 37]	90	SMD 0.03 (-0.38, 0.45)	0.88	0.94	0.33	0
Quality of life	4 [21, 29, 34, 38]	322	SMD 0.06 (-0.14, 0.25)	0.57	1.4	0.41	0
Anxiety	3 [21, 31, 37]	171	SMD -0.23 (-0.54, 0.08)	0.14	1.19	0.76	0
Depression	2 [21, 31]	121	WMD -0.23 (-1.49, 1.02)	0.71	0.86	0.65	0
Bifidobacteria	3 [29, 31, 35]	200	WMD 1.16 (0.06, 2.26)	**0.04**	24.3	<0.00001	92
Lactobacilli	2 [29, 31]	164	WMD 0.22 (-0.31, 0.75)	0.41	2.94	0.09	66
Adverse events	4 [21, 36-38]	355	OR 0.77 (0.47, 1.26)	0.30	2.25	0.69	0

FIGURE LEGENDS

Figure 1: PRISMA flow diagram of studies in systematic review.

Figure 2: Forest plot of integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.

Figure 3: Forest plot of subgroup analysis of prebiotic type (inulin type fructan *versus* non-inulin type fructan) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.

Figure 4: Forest plot of subgroup analysis of different prebiotic dose (≤6 g/d vs >6 g/d) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.

Figure 5: Forest plot of absolute abundance of fecal bifidobacteria and lactobacilli in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as weighted mean differences (95% CI) using a random effects model.

Figure 6: Risk of bias in A: individual studies and B: overall for each category of randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD.

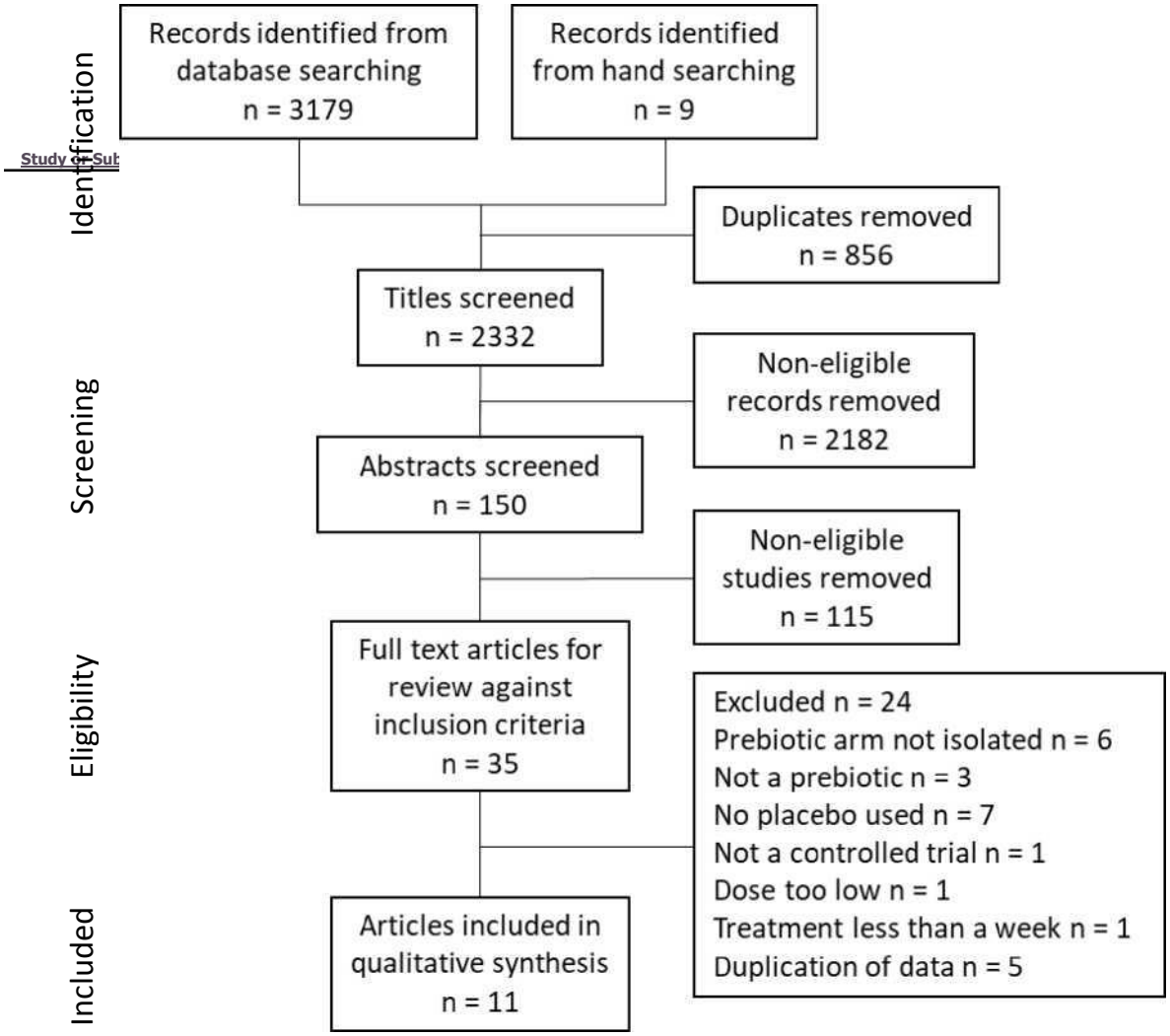

Identification
Screening
Eligibility
Included
Records identified from database searching n = 3179
Records identified from hand searching n = 9
Duplicates removed n = 856
Titles screened n = 2332
Non-eligible records removed n = 2182
Abstracts screened n = 150
Non-eligible studies removed n = 115
Full text articles for review against inclusion criteria n = 35
Excluded n = 24
Prebiotic arm not isolated n = 6
Not a prebiotic n = 3
No placebo used n = 7
Not a controlled trial n = 1
Dose too low n = 1
Treatment less than a week n = 1
Duplication of data n = 5
Articles included in qualitative synthesis n = 11

Figure 1

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Integrative symptom score				
Azpiroz 2017b [31]	0.1562	0.2284	1 2.8%	0.1 6 [-0.29, 0.60]
Niv 2016 [38]	-0.11 59	0.1 934	12.9%	-0.12 [-0.49, 0.26]
Olesen 2000 [36]	0.2022	0.2048	1 2.8%	0.20 [-0.20, 0.60]
Shepherd 2008 [32]	1.1 533	0.3294	12.5%	1.1 5 [0.51,1.80]
Silk 2009 high dose [21]	0.1257	0.4633	11.9%	0.13 [-0.78,1.03]
Silk 2009 low dose [21]	-0.5502	0.4604	11.9%	-0.55 [-1.45, 0.35]
Vulevic 2018 [34]	-3.8025	0.2601	12.7%	-3.80 [-4.31, -3.29]
Xu 201 5 [29]	-0.265	13.296	12.6%	-0.27 [-0.85, 0.32]
Subtotal (95% CI)			**100.0%**	**-0.39[-1.43, 064**
Heterogeneity: Tau' = 2.13; Chi'= 211.70, df= 7 (P < 0.00001); I² = 97%				
Testfor overall effect Z = 0 74 (P- 0 46)				
1.1.2 Abdominal pain				
Azpiroz 2017b [31]	0.31 99	0.2296	1 0.2%	0.32 [-0.1 3, 0.77]
Isakov 2013 [30]	-0.7276	0.3265	1 0.0%	-0.73 [-1.37, -0.09]
Niv 2016 [38]	-0.053	0.1 933	1 0.3%	-0.05 [-0.43, 0.33]
Olesen 2000 [36]	0.2075	0.2487	1 0.2%	0.21 [-0.28, 0.69]
Paine.au 2008 [37]	-0.7363	0.2925	1 0.1 %	-0.74 [-1.31, -0.1 6]
Shepherd 2008 [32]	1.031 3	0.3247	1 0.0%	1.03 [0.39,1.67]
Silk: 2009 high dose [21]	-0.3924	0.4669	9.6%	-0.39 [-1.31,0.52]
Silk 2009 low dose [21]	-0.8525	0.4703	9.6%	-0.85 [-1.77, 0.07]
Vulevic 2018 [34]	-7.0145	0.4151	9.8%	-7.01 [-7.83,-6.20]
Xu 201 5 [29]	-0.295	0.2159	1 0.2%	-0.29 [-0.72, 0.1 3]
Subtotal (95% CI)			**100.0%**	**-0.83 [-1.84, 0.18]**
Heterogeneity: Tau² = 2.56; Chi'= 295.85, df= 9 (P < 0.00001); I²= **97%**				
Test for overall *effect* Z = 1 61 (P = **0** 11)				
1.1.3 Bloating				
Isakov 2013 [30]	0.1975	0.317	11.1 %	0.20 [-0.42, 0.82]
Niv 2016 [38]	-0.2301	0.1 939	11.4%	-0.23 [-0.61,0.1 5]
Olesen 2000 [36]	0.2484	0.2492	11.3%	0.25 [-0.24, 0.74]
Paine.au 2008 [37]	-0.1271	0.2833	11.2%	-0.13 [-0.68, 0.43]
Shepherd 2008 [32]	1.1 533	0.3294	11.1 %	1.1 5 [0.51,1.80]
Silk 2009 high dose [21]	0.448	0.468	1 0.7%	0.45 [-0.47,1.37]
Silk 2009 low dose [21]	-0.611 6	0.462	1 0.7%	-0.61 [-1.52,0.29]
Vulevic 2018 [34]	-5.7464	0.351 5	11.1 %	-5.75 [-6.44,-5.06]
Xu 2015 [29]	-0.5257	0.2184	11.4%	-0.53 [-0.95, -0.1 0]
Subtotal (95% CI)			**100.0%**	**-0.57 [-1.67, 0.52]**
Heterogeneity: Tau²= 2.72; Chi³ = 269.26, df= 8 (P < 0.00001); P= 97%				
Test for overall effect: Z = 1.03 (P = 0.30)				
1.1.4 Flatulence				
Niv 2016 [38]	-0.3042	0.1944	17.0%	-0.30 [-0.69, 0.08]
Olesen 2000 [36]	0.5662	0.2587	16.9%	0.57 [0.06,1.07]
Shepherd 2008 [32]	1.2053	0.331 6	16.7%	1.21 [0.56,1.86]
Silk: 2009 high dose [21]	-0.21 84	0.4641	16.2%	-0.22 [-1.1 3, 0.69]
Silk 2009 low dose [21]	-0.6347	0.4627	16.2%	-0.63 [-1.54, 0.27]
Vulevic 2018 [34]	-3.771 2	0.2587	1 6.9%	-3.77 [-4.28,-3.26]
Subtotal (95% CI)			**100.0%**	**-0.53 [-2.04,**
Heterogeneity: Tau'= 3.43; Chi³ 203.00, df= 5 (P < 0.00001); I== 98%				
Test for overall effect: Z = 0.69 (P = 0.49)				

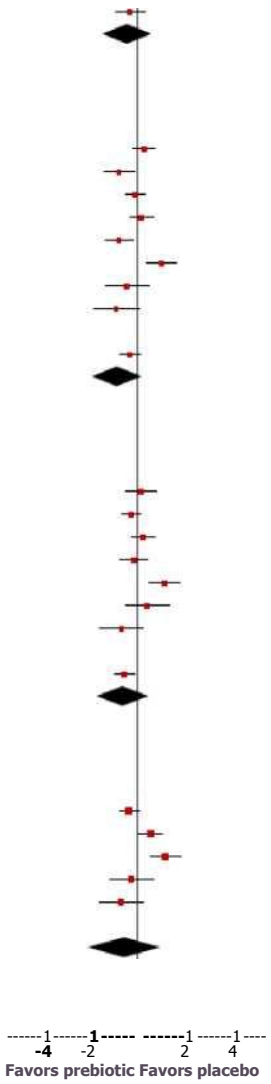


Figure 2

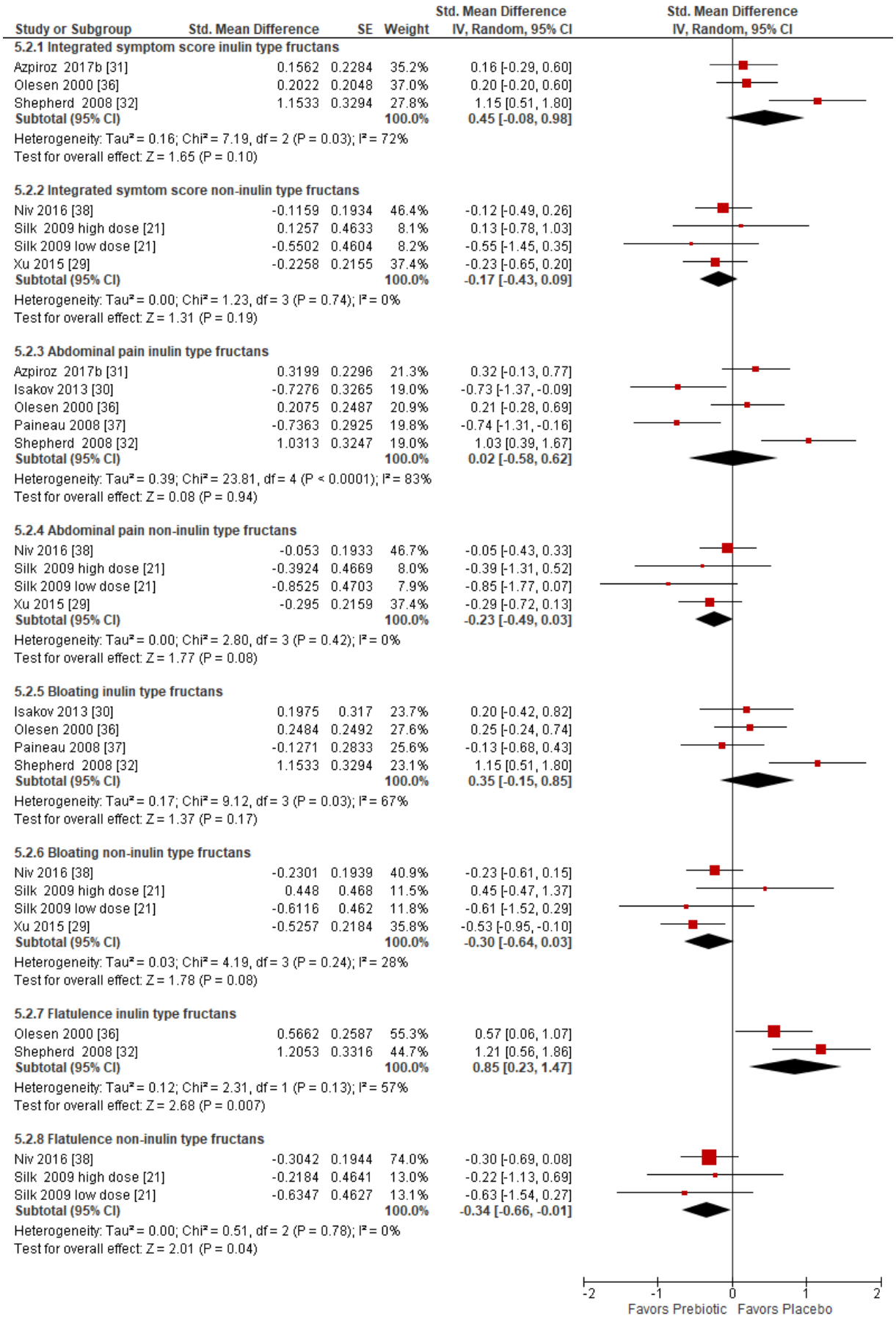

Study or Subgroup
Std. Mean Difference
SE
Weight
Std. Mean Difference IV, Random, 95% CI
Std. Mean Difference IV, Random, 95% CI
5.2.1 Integrated symptom score inulin type fructans
Azpiroz 2017b [31] 0.1562 0.2284 35.2% 0.16 [-0.29, 0.60]
Olesen 2000 [36] 0.2022 0.2048 37.0% 0.20 [-0.20, 0.60]
Shepherd 2008 [32] 1.1533 0.3294 27.8% 1.15 [0.51, 1.80]
Subtotal (95% CI) 100.0% 0.45 [-0.08, 0.98]
Heterogeneity: Tau² = 0.16; Chi² = 7.19, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 1.65 (P = 0.10)
5.2.2 Integrated symtom score non-inulin type fructans
Niv 2016 [38] -0.1159 0.1934 46.4% -0.12 [-0.49, 0.26]
Silk 2009 high dose [21] 0.1257 0.4633 8.1% 0.13 [-0.78, 1.03]
Silk 2009 low dose [21] -0.5502 0.4604 8.2% -0.55 [-1.45, 0.35]
Xu 2015 [29] -0.2258 0.2155 37.4% -0.23 [-0.65, 0.20]
Subtotal (95% CI) 100.0% -0.17 [-0.43, 0.09]
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 3 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)
5.2.3 Abdominal pain inulin type fructans
Azpiroz 2017b [31] 0.3199 0.2296 21.3% 0.32 [-0.13, 0.77]
Isakov 2013 [30] -0.7276 0.3265 19.0% -0.73 [-1.37, -0.09]
Olesen 2000 [36] 0.2075 0.2487 20.9% 0.21 [-0.28, 0.69]
Paineau 2008 [37] -0.7363 0.2925 19.8% -0.74 [-1.31, -0.16]
Shepherd 2008 [32] 1.0313 0.3247 19.0% 1.03 [0.39, 1.67]
Subtotal (95% CI) 100.0% 0.02 [-0.58, 0.62]
Heterogeneity: Tau² = 0.39; Chi² = 23.81, df = 4 (P < 0.0001); I² = 83%
Test for overall effect: Z = 0.08 (P = 0.94)
5.2.4 Abdominal pain non-inulin type fructans
Niv 2016 [38] -0.053 0.1933 46.7% -0.05 [-0.43, 0.33]
Silk 2009 high dose [21] -0.3924 0.4669 8.0% -0.39 [-1.31, 0.52]
Silk 2009 low dose [21] -0.8525 0.4703 7.9% -0.85 [-1.77, 0.07]
Xu 2015 [29] -0.295 0.2159 37.4% -0.29 [-0.72, 0.13]
Subtotal (95% CI) 100.0% -0.23 [-0.49, 0.03]
Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)
5.2.5 Bloating inulin type fructans
Isakov 2013 [30] 0.1975 0.317 23.7% 0.20 [-0.42, 0.82]
Olesen 2000 [36] 0.2484 0.2492 27.6% 0.25 [-0.24, 0.74]
Paineau 2008 [37] -0.1271 0.2833 25.6% -0.13 [-0.68, 0.43]
Shepherd 2008 [32] 1.1533 0.3294 23.1% 1.15 [0.51, 1.80]
Subtotal (95% CI) 100.0% 0.35 [-0.15, 0.85]
Heterogeneity: Tau² = 0.17; Chi² = 9.12, df = 3 (P = 0.03); I² = 67%
Test for overall effect: Z = 1.37 (P = 0.17)
5.2.6 Bloating non-inulin type fructans
Niv 2016 [38] -0.2301 0.1939 40.9% -0.23 [-0.61, 0.15]
Silk 2009 high dose [21] 0.448 0.468 11.5% 0.45 [-0.47, 1.37]
Silk 2009 low dose [21] -0.6116 0.462 11.8% -0.61 [-1.52, 0.29]
Xu 2015 [29] -0.5257 0.2184 35.8% -0.53 [-0.95, -0.10]
Subtotal (95% CI) 100.0% -0.30 [-0.64, 0.03]
Heterogeneity: Tau² = 0.03; Chi² = 4.19, df = 3 (P = 0.24); I² = 28%
Test for overall effect: Z = 1.78 (P = 0.08)
5.2.7 Flatulence inulin type fructans
Olesen 2000 [36] 0.5662 0.2587 55.3% 0.57 [0.06, 1.07]
Shepherd 2008 [32] 1.2053 0.3316 44.7% 1.21 [0.56, 1.86]
Subtotal (95% CI) 100.0% 0.85 [0.23, 1.47]
Heterogeneity: Tau² = 0.12; Chi² = 2.31, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 2.68 (P = 0.007)
5.2.8 Flatulence non-inulin type fructans
Niv 2016 [38] -0.3042 0.1944 74.0% -0.30 [-0.69, 0.08]
Silk 2009 high dose [21] -0.2184 0.4641 13.0% -0.22 [-1.13, 0.69]
Silk 2009 low dose [21] -0.6347 0.4627 13.1% -0.63 [-1.54, 0.27]
Subtotal (95% CI) 100.0% -0.34 [-0.66, -0.01]
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)
-2
-1
0
1
2
Favors Prebiotic
Favors Placebo

Figure 3

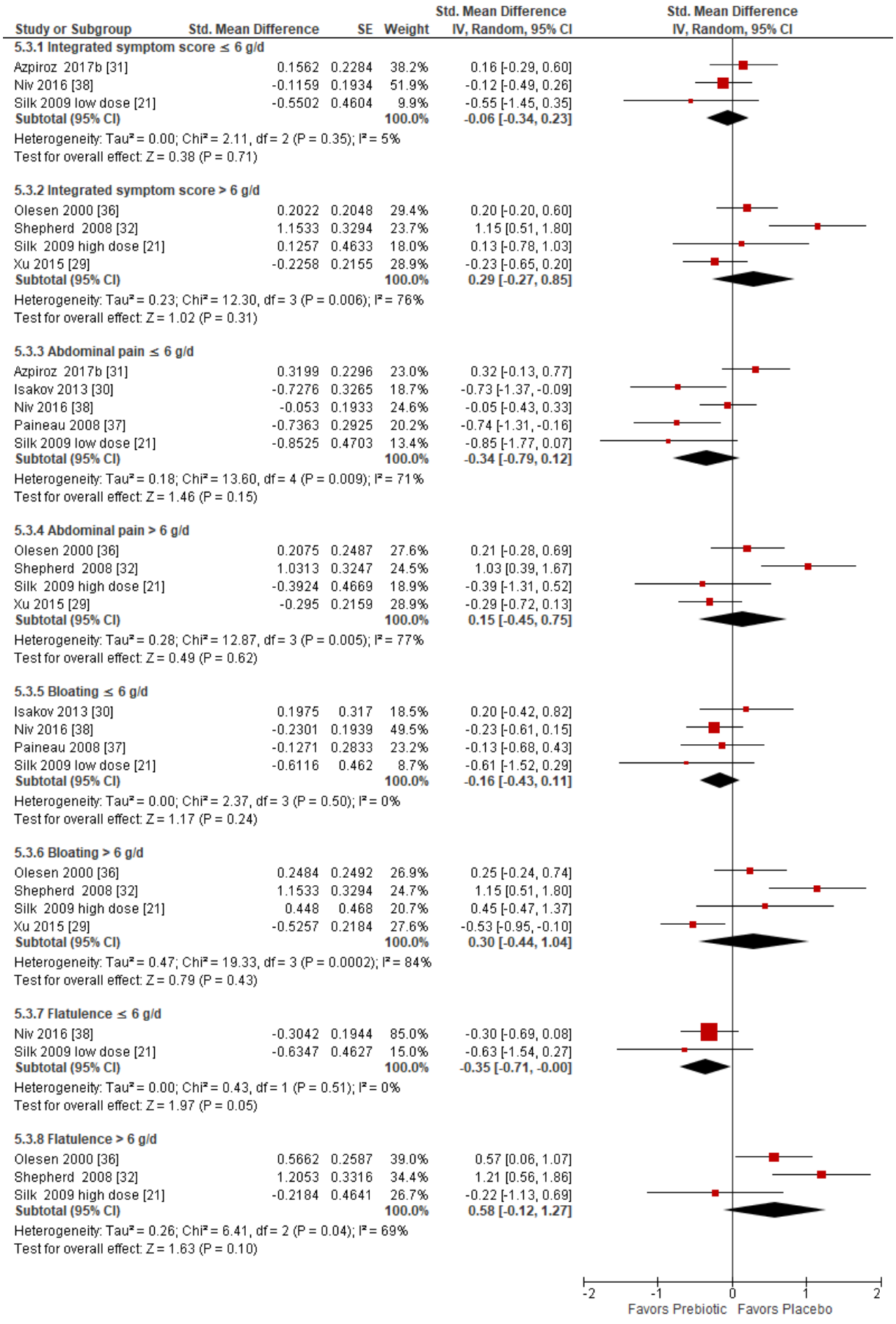

Study or Subgroup
Std. Mean Difference
SE
Weight
Std. Mean Difference IV, Random, 95% CI
Std. Mean Difference IV, Random, 95% CI
5.3.1 Integrated symptom score ≤ 6 g/d
Azpiroz 2017b [31] 0.1562 0.2284 38.2% 0.16 [-0.29, 0.60]
Niv 2016 [38] -0.1159 0.1934 51.9% -0.12 [-0.49, 0.26]
Silk 2009 low dose [21] -0.5502 0.4604 9.9% -0.55 [-1.45, 0.35]
Subtotal (95% CI) 100.0% -0.06 [-0.34, 0.23]
Heterogeneity: Tau² = 0.00; Chi² = 2.11, df = 2 (P = 0.35); I² = 5%
Test for overall effect: Z = 0.38 (P = 0.71)
5.3.2 Integrated symptom score > 6 g/d
Olesen 2000 [36] 0.2022 0.2048 29.4% 0.20 [-0.20, 0.60]
Shepherd 2008 [32] 1.1533 0.3294 23.7% 1.15 [0.51, 1.80]
Silk 2009 high dose [21] 0.1257 0.4633 18.0% 0.13 [-0.78, 1.03]
Xu 2015 [29] -0.2258 0.2155 28.9% -0.23 [-0.65, 0.20]
Subtotal (95% CI) 100.0% 0.29 [-0.27, 0.85]
Heterogeneity: Tau² = 0.23; Chi² = 12.30, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 1.02 (P = 0.31)
5.3.3 Abdominal pain ≤ 6 g/d
Azpiroz 2017b [31] 0.3199 0.2296 23.0% 0.32 [-0.13, 0.77]
Isakov 2013 [30] -0.7276 0.3265 18.7% -0.73 [-1.37, -0.09]
Niv 2016 [38] -0.053 0.1933 24.6% -0.05 [-0.43, 0.33]
Paineau 2008 [37] -0.7363 0.2925 20.2% -0.74 [-1.31, -0.16]
Silk 2009 low dose [21] -0.8525 0.4703 13.4% -0.85 [-1.77, 0.07]
Subtotal (95% CI) 100.0% -0.34 [-0.79, 0.12]
Heterogeneity: Tau² = 0.18; Chi² = 13.60, df = 4 (P = 0.009); I² = 71%
Test for overall effect: Z = 1.46 (P = 0.15)
5.3.4 Abdominal pain > 6 g/d
Olesen 2000 [36] 0.2075 0.2487 27.6% 0.21 [-0.28, 0.69]
Shepherd 2008 [32] 1.0313 0.3247 24.5% 1.03 [0.39, 1.67]
Silk 2009 high dose [21] -0.3924 0.4669 18.9% -0.39 [-1.31, 0.52]
Xu 2015 [29] -0.295 0.2159 28.9% -0.29 [-0.72, 0.13]
Subtotal (95% CI) 100.0% 0.15 [-0.45, 0.75]
Heterogeneity: Tau² = 0.28; Chi² = 12.87, df = 3 (P = 0.005); I² = 77%
Test for overall effect: Z = 0.49 (P = 0.62)
5.3.5 Bloating ≤ 6 g/d
Isakov 2013 [30] 0.1975 0.317 18.5% 0.20 [-0.42, 0.82]
Niv 2016 [38] -0.2301 0.1939 49.5% -0.23 [-0.61, 0.15]
Paineau 2008 [37] -0.1271 0.2833 23.2% -0.13 [-0.68, 0.43]
Silk 2009 low dose [21] -0.6116 0.462 8.7% -0.61 [-1.52, 0.29]
Subtotal (95% CI) 100.0% -0.16 [-0.43, 0.11]
Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)
5.3.6 Bloating > 6 g/d
Olesen 2000 [36] 0.2484 0.2492 26.9% 0.25 [-0.24, 0.74]
Shepherd 2008 [32] 1.1533 0.3294 24.7% 1.15 [0.51, 1.80]
Silk 2009 high dose [21] 0.448 0.468 20.7% 0.45 [-0.47, 1.37]
Xu 2015 [29] -0.5257 0.2184 27.6% -0.53 [-0.95, -0.10]
Subtotal (95% CI) 100.0% 0.30 [-0.44, 1.04]
Heterogeneity: Tau² = 0.47; Chi² = 19.33, df = 3 (P = 0.0002); I² = 84%
Test for overall effect: Z = 0.79 (P = 0.43)
5.3.7 Flatulence ≤ 6 g/d
Niv 2016 [38] -0.3042 0.1944 85.0% -0.30 [-0.69, 0.08]
Silk 2009 low dose [21] -0.6347 0.4627 15.0% -0.63 [-1.54, 0.27]
Subtotal (95% CI) 100.0% -0.35 [-0.71, -0.00]
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
5.3.8 Flatulence > 6 g/d
Olesen 2000 [36] 0.5662 0.2587 39.0% 0.57 [0.06, 1.07]
Shepherd 2008 [32] 1.2053 0.3316 34.4% 1.21 [0.56, 1.86]
Silk 2009 high dose [21] -0.2184 0.4641 26.7% -0.22 [-1.13, 0.69]
Subtotal (95% CI) 100.0% 0.58 [-0.12, 1.27]
Heterogeneity: Tau² = 0.26; Chi² = 6.41, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 1.63 (P = 0.10)
-2
-1
0
1
2
Favors Prebiotic
Favors Placebo

Figure 4

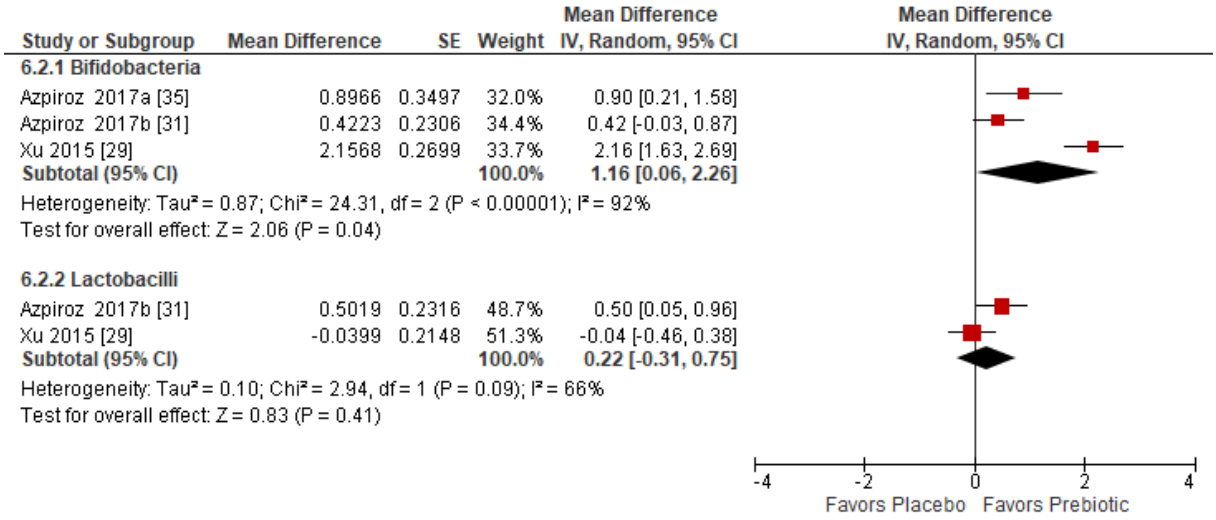
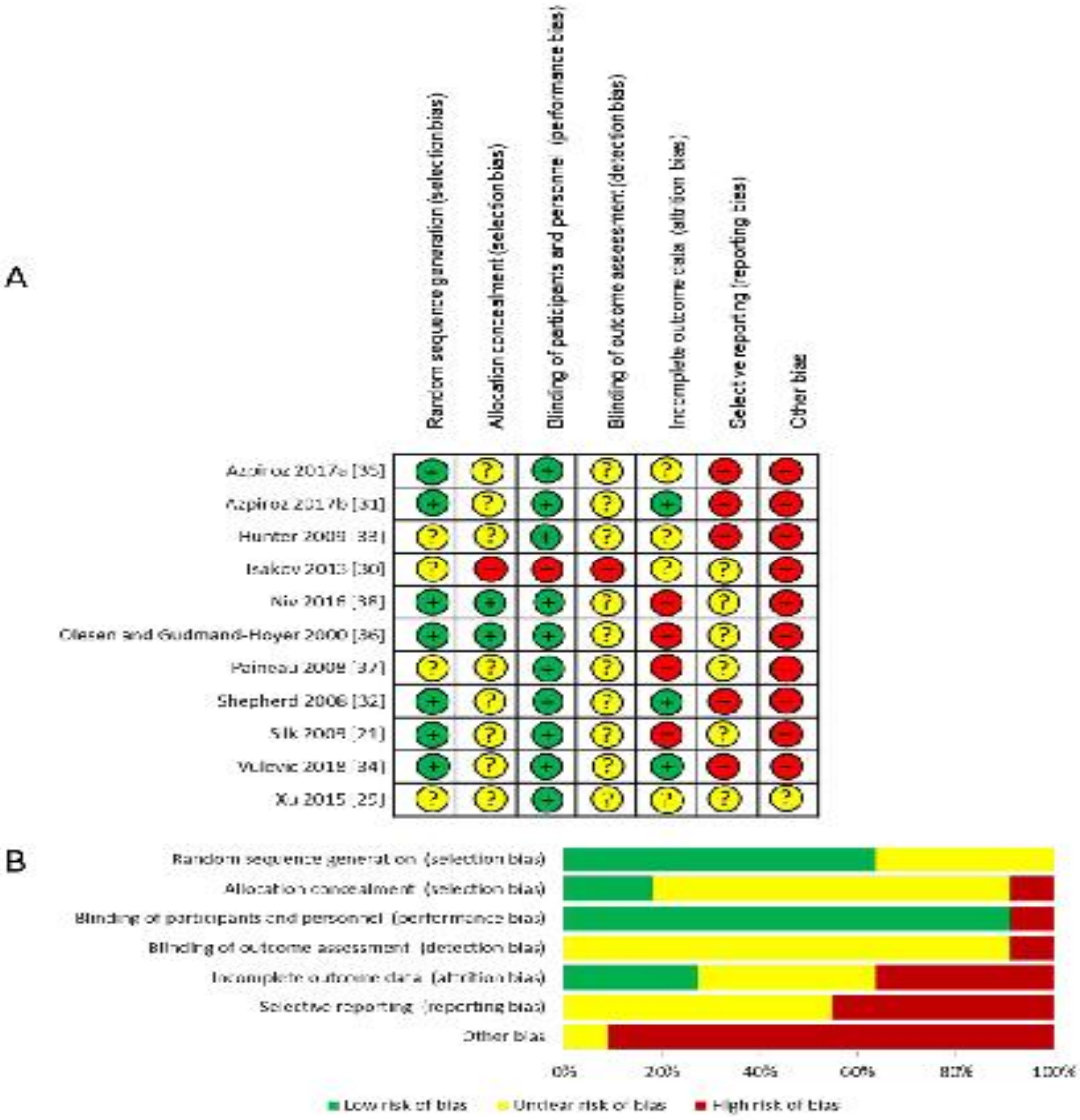

Study or Subgroup
Mean Difference
SE
Weight
Mean Difference
IV, Random, 95% CI
Mean Difference
IV, Random, 95% CI
6.2.1 Bifidobacteria
Azpiroz 2017a [35] 0.8966 0.3497 32.0% 0.90 [0.21, 1.58]
Azpiroz 2017b [31] 0.4223 0.2306 34.4% 0.42 [-0.03, 0.87]
Xu 2015 [29] 2.1568 0.2699 33.7% 2.16 [1.63, 2.69]
Subtotal (95% CI) 100.0% 1.16 [0.06, 2.26]
Heterogeneity: Tau² = 0.87; Chi² = 24.31, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.06 (P = 0.04)
6.2.2 Lactobacilli
Azpiroz 2017b [31] 0.5019 0.2316 48.7% 0.50 [0.05, 0.96]
Xu 2015 [29] -0.0399 0.2148 51.3% -0.04 [-0.46, 0.38]
Subtotal (95% CI) 100.0% 0.22 [-0.31, 0.75]
Heterogeneity: Tau² = 0.10; Chi² = 2.94, df = 1 (P = 0.09); I² = 66%
Test for overall effect: Z = 0.83 (P = 0.41)
-4
-2
0
2
4
Favors Placebo
Favors Prebiotic

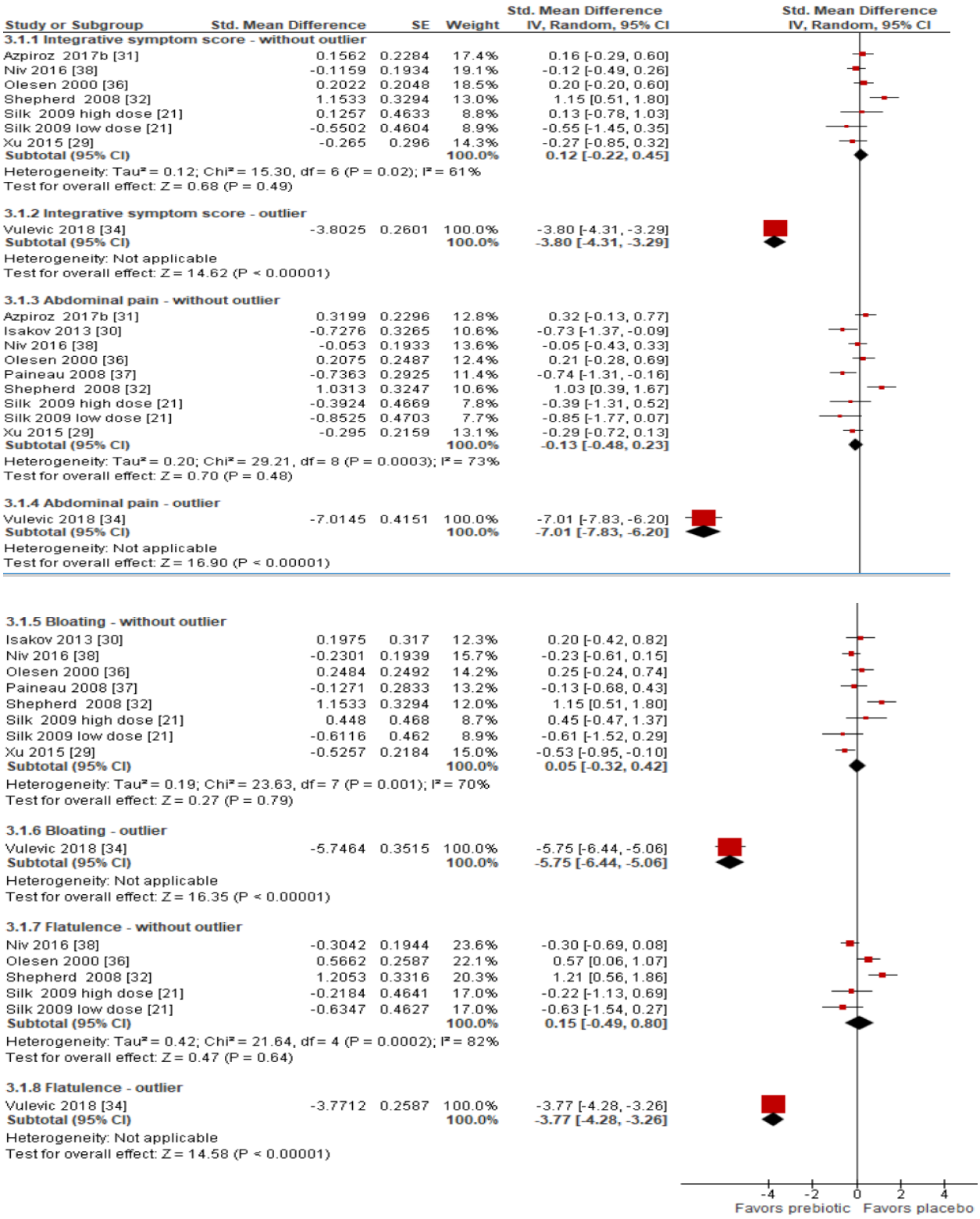
Figure 5


A
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Azpiroz 2017a [35]
Azpiroz 2017b [33]
Hunter 2008 [31]
Isakov 2013 [30]
Niv 2016 [38]
Olesen and Gudmand-Hoyer 2000 [36]
Poineau 2009 [37]
Shepherd 2006 [32]
Silk 2009 [21]
Vulevic 2013 [34]
Xu 2015 [25]
B
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
20%
40%
60%
80%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

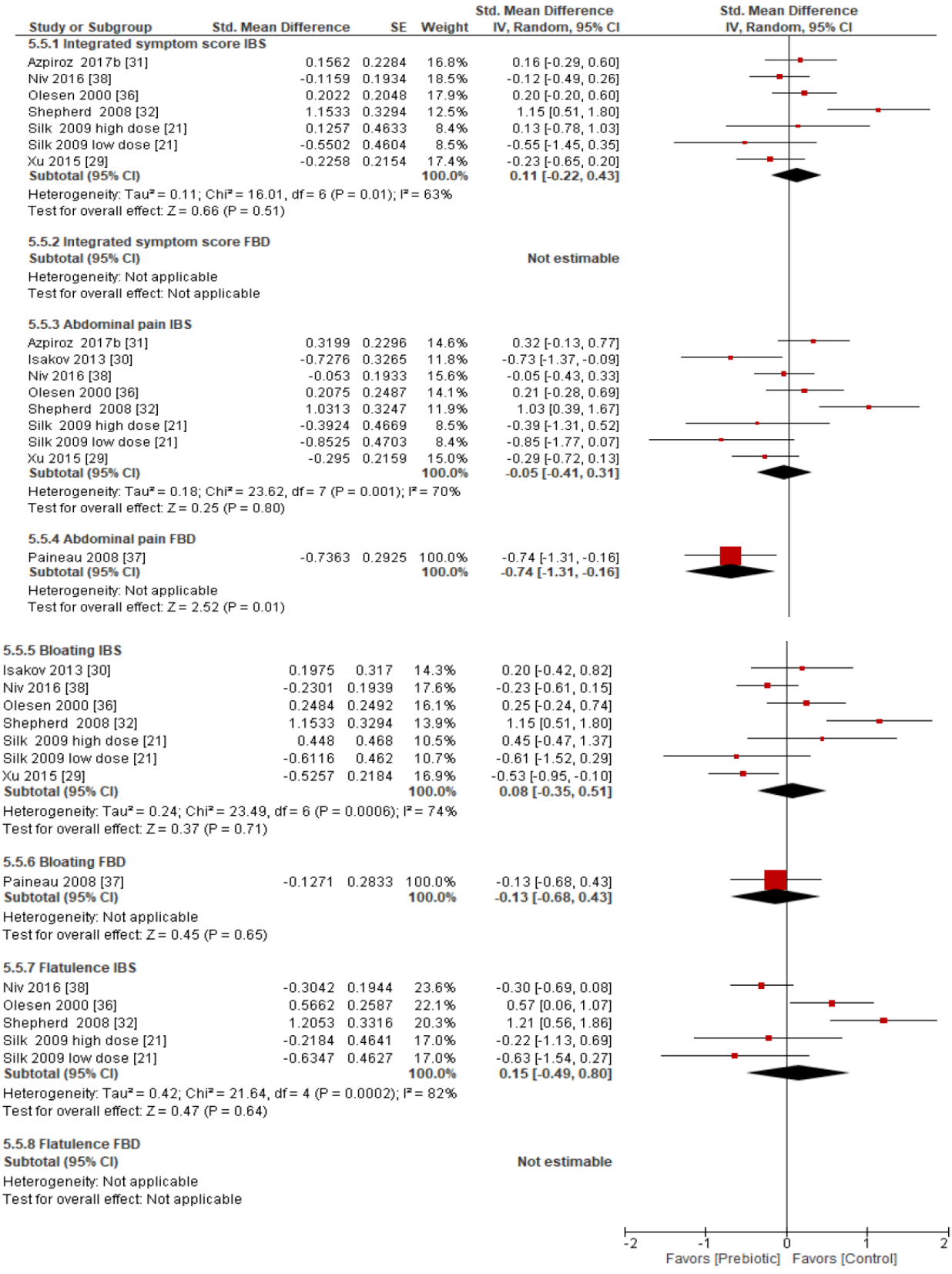
Supplemental table 1

Detailed Search Strategy Embase 1947 to 2018 November 8

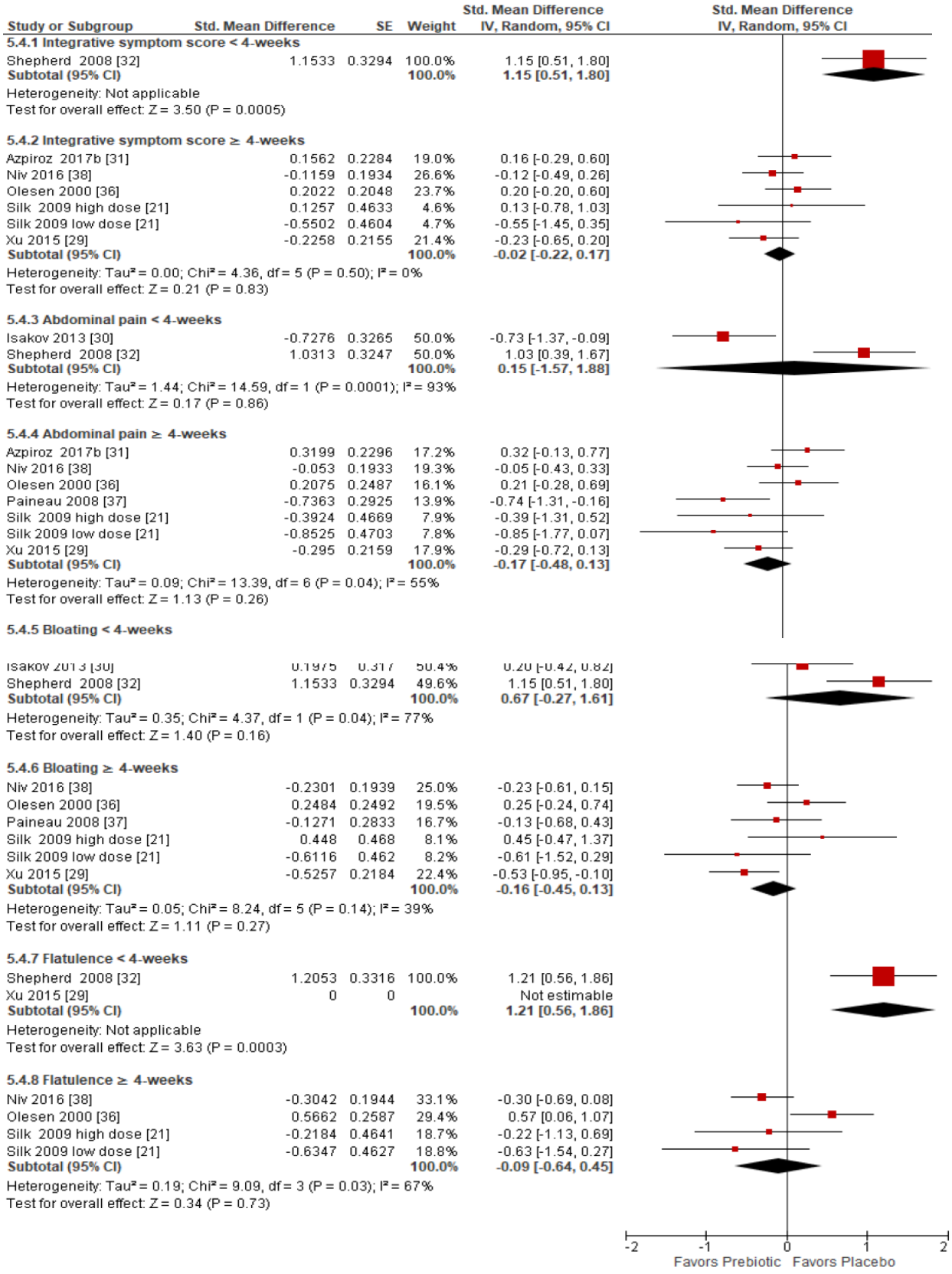
Prebiotic agent/ OR prebiotic*.mp. OR exp inulin/ OR inulin.mp. OR inulin type fruct*.mp. OR chicory.mp. OR exp chicory/ OR exp fructan/ OR fructan*.mp. OR fructo-oligosaccharide*.mp. OR fructooligosaccharide*.mp. OR oligofructose.mp. OR exp oligomer/ or oligomers.mp. OR large size polymer*.mp. OR exp oligosaccharide/ or oligosaccharide*.mp. OR galactooligosaccharide*.mp. OR galacto-oligosaccharide*.mp. OR trans-galactooligosaccharide*.mp. OR soya-oligosaccharide*.mp. OR partially hydrolysed guar gum.mp. OR sc-FOS.mp. OR fermentable.mp.
AND
irritable bowel syndrome.mp. OR functional bowel disorder.mp. OR functional bloating.mp. OR functional diarr*.mp. OR IBS.mp. OR IBS?C.mp. OR IBS-C.mp. OR IBS?D.mp. OR IBS-D.mp. OR IBS?U.mp. OR IBS?M.mp. OR IBS-U.mp. OR IBS-M.mp.
Limit to human studies, limit to "not review"



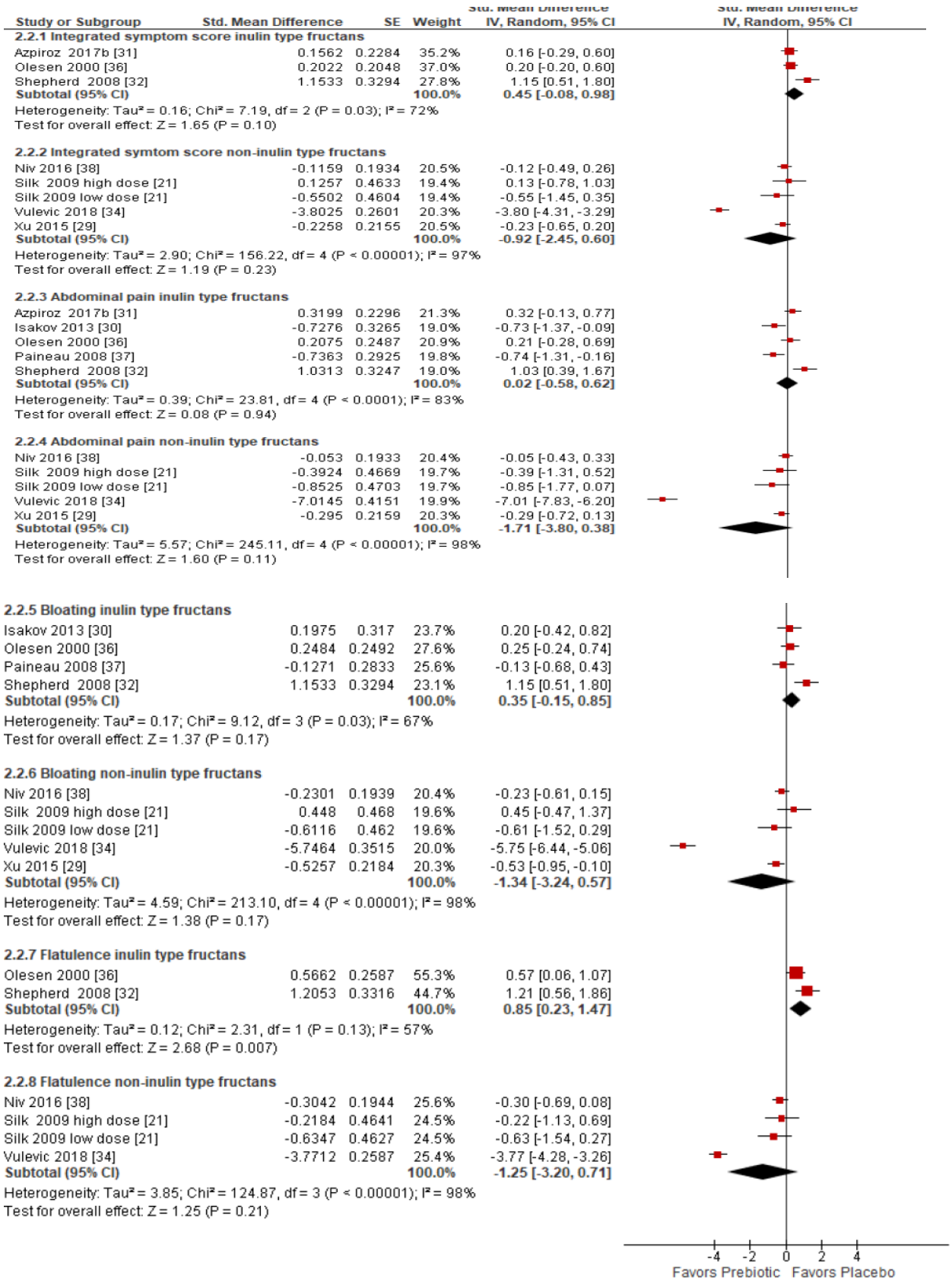
Supplemental figure 1 Forest plot of integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with irritable bowel syndrome (IBS) or other functional bowel disorder (FBD) with outlier study separated. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.



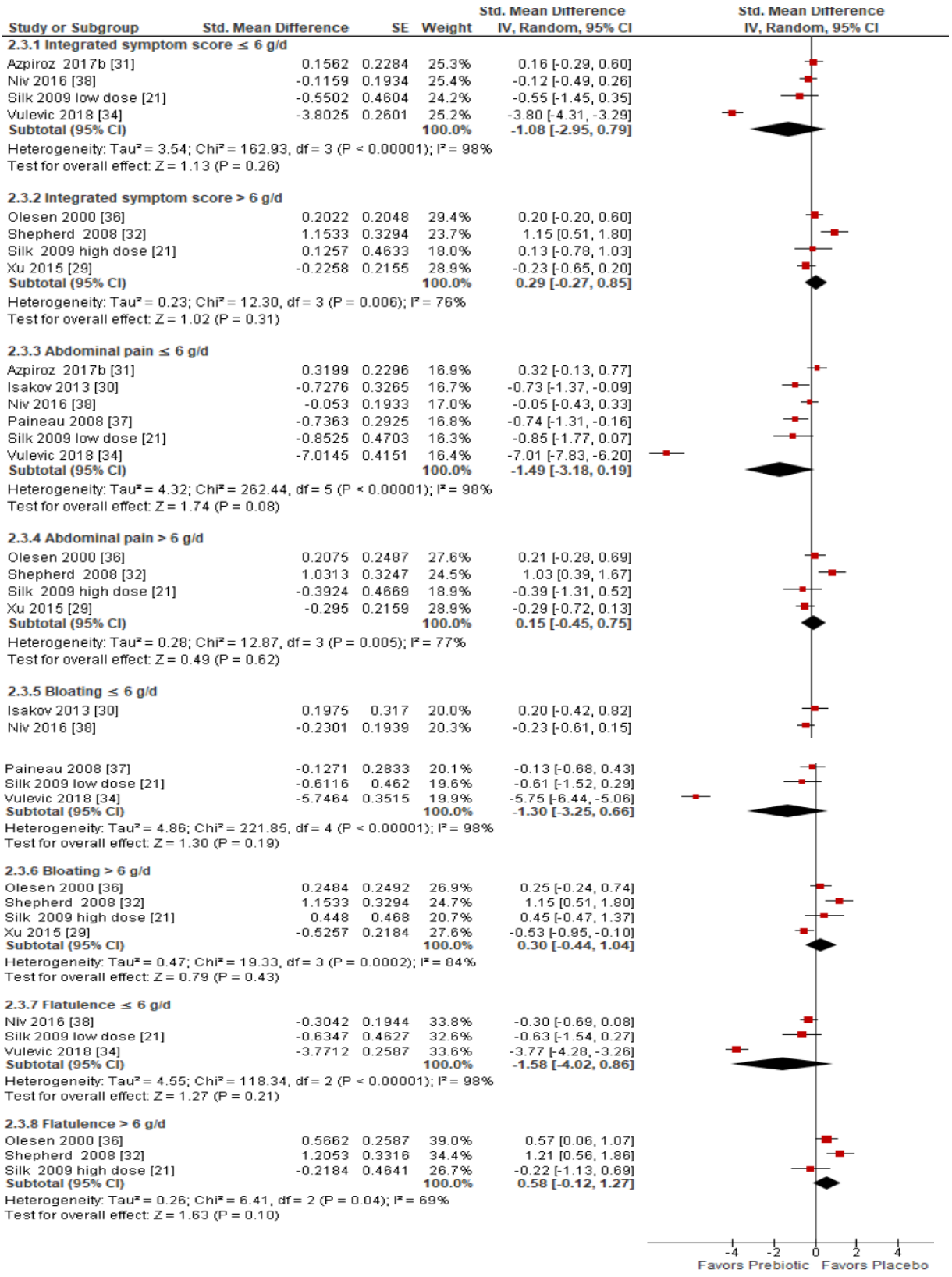
Supplemental figure 2 Forest plot of subgroup analysis of bowel disorder type IBS vs other FBD on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.



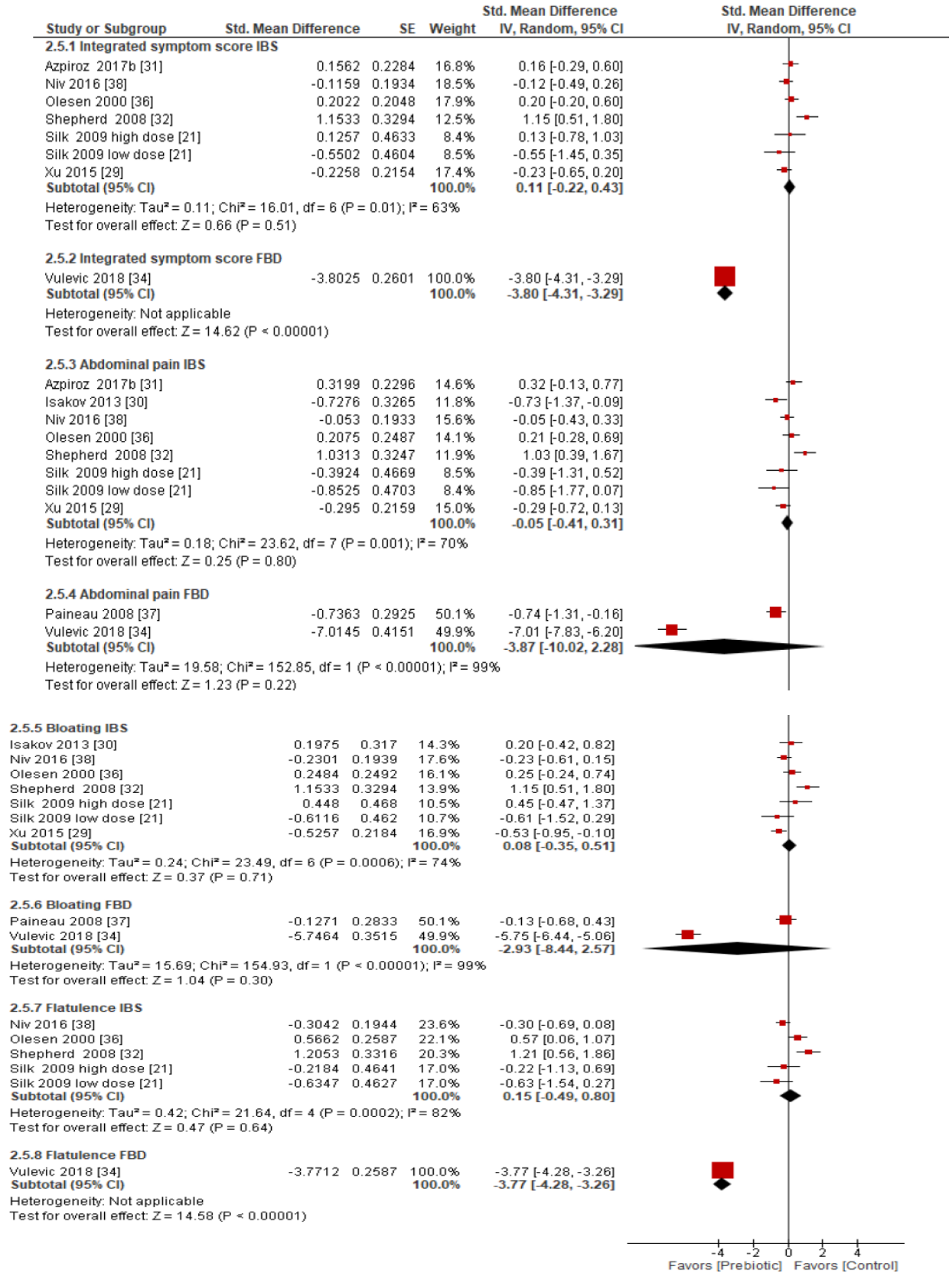
Supplemental figure 3 Forest plot of subgroup analysis of prebiotic duration (<4 weeks vs ≥4 weeks) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.



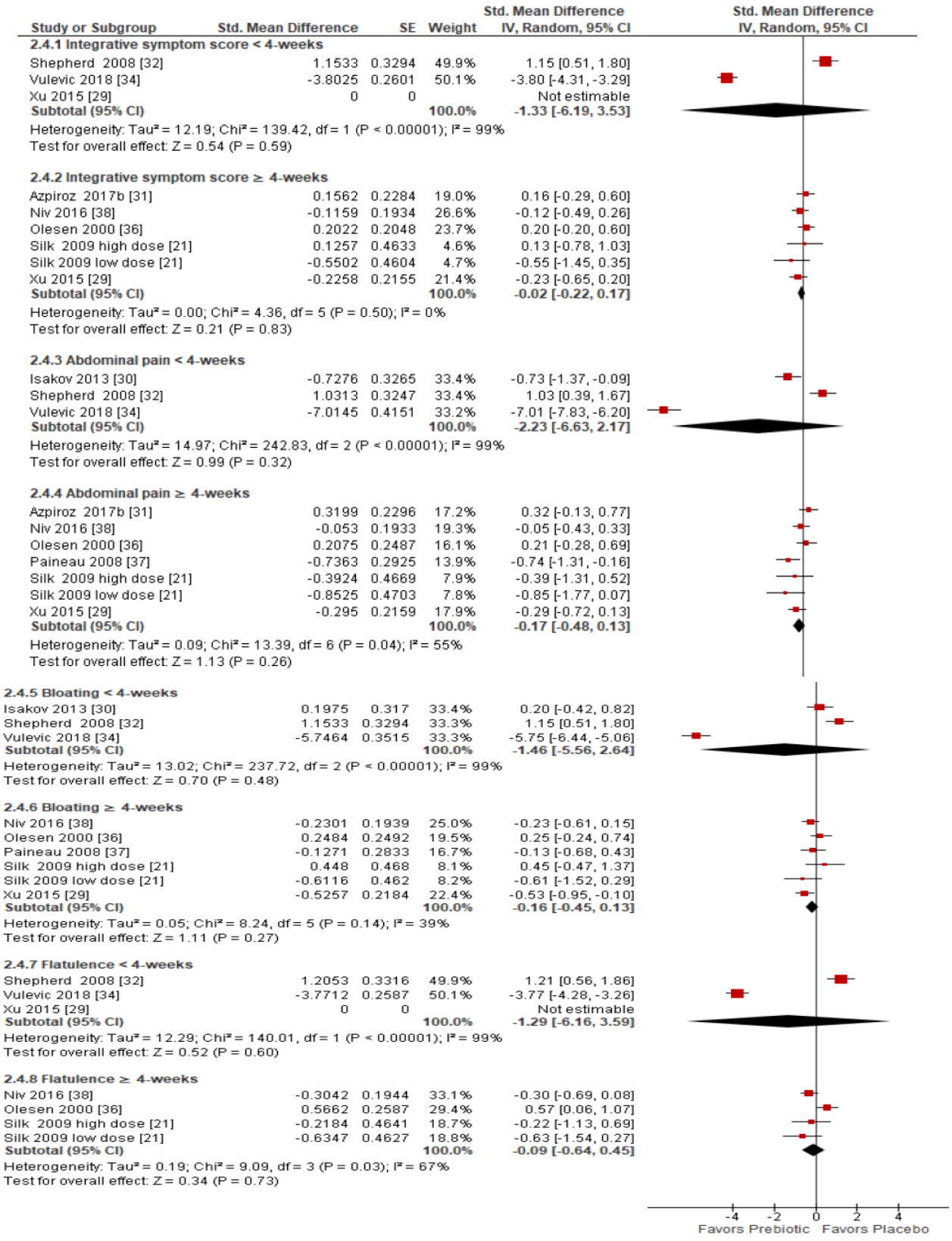
Supplemental figure 4 Forest plot of subgroup analysis of prebiotic type (inulin type fructan *versus* non-inulin type fructan) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model. The outlier study is included in the forest plot.



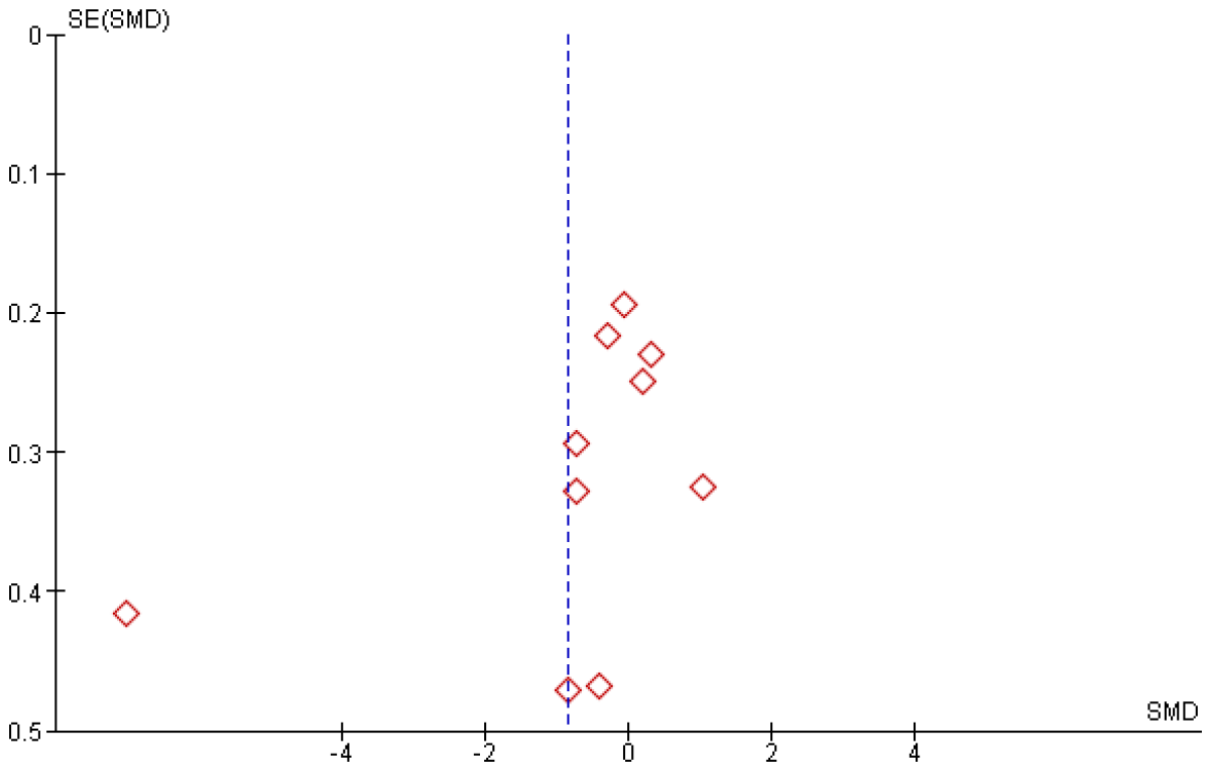
Supplemental figure 5 Forest plot of subgroup analysis of different prebiotic dose (≤6 g/d vs >6 g/d) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model. The outlier study is included in the forest plot.



Supplemental figure 6 Forest plot of subgroup analysis of bowel disorder type IBS vs other FBD on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model. The outlier study is included in the forest plot.



Supplemental figure 7 Forest plot of subgroup analysis of prebiotic duration (<4 weeks vs ≥4 weeks) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model. The outlier study is included in the forest plot.



Supplemental figure 8 Funnel plot of abdominal pain outcome in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD.